5.01 ABALOPARATIDE, Solution for injection 3 mg in 1.5 mL pre-filled pen, Eladynos®, THERAMEX AUSTRALIA PTY LTD.

1 Purpose of submission

1.1 The Category 2 submission requested a General Schedule listing of abaloparatide as an alternative first-line treatment for patients with severe established osteoporosis and very high risk of fracture, regardless of gender.

1.2 Listing was requested based on a cost-minimisation approach (CMA) to derive the proposed price of abaloparatide, such that the total cost of treatment over one complete treatment course (based on a maximum 18 months of treatment) is equivalent to a duration of treatment with romosozumab (the comparator, consisting of up to 12 months of treatment). This approach mirrored the price derivation used to set the price of romosozumab as second-line therapy versus teriparatide when it was considered at the March 2020 PBAC meeting using a CMA.

Table 1: Key components of the clinical issue addressed by the submission

Component	Description
Population	Severe established osteoporosis. Patient must be at a very high risk of fracture. First-line treatment.
Intervention	Abaloparatide (Eladynos) SC daily injection, 3 mg/1.5 mL pre-filled pen
Comparator	Romosozumab (Evenity) SC monthly injection, 105 mg/1.17 mL, 2 x 1.17 mL pre-filled syringes
Outcomes	Primary: • Incidence of new vertebral fractures. Secondary: • Incidence of nonvertebral fractures • Incidence of clinical fractures • Safety outcomes
Clinical claim	Abaloparatide is non-inferior to romosozumab, in the first-line treatment of the requested PBS population. Abaloparatide has a superior safety profile compared with romosozumab.

Source: Table 1-2, p11 of the submission.
BMD = bone mineral density; SC = subcutaneous

2 Background

Registration status

2.1 Abaloparatide was approved by the Therapeutic Goods Administration (TGA) for the indication of treating osteoporosis in postmenopausal women at increased risk of fracture in November 2024.

Previous PBAC consideration

2.2 The PBAC previously recommended the listing of teriparatide in November 2008 for the treatment of severe established osteoporosis in the second line setting on the basis of acceptable cost-effectiveness over alendronate in the context of a very high clinical need (p5, teriparatide Public Summary Document [PSD], November 2008).

2.3 The PBAC previously recommended the listing of romosozumab (second-line) in March 2020 for the treatment of severe osteoporosis in patients who have experienced a prior fracture while on anti-resorptive therapy (ART) for >12 months on the basis of a CMA compared to teriparatide (paragraphs 1.2 and 7.1, romosozumab PSD, March 2020). In March 2024, the PBAC recommended the listing romosozumab (first-line) for the treatment of severe osteoporosis on the basis of a CMA versus alendronate. This was accepted with indication-specific pricing and a Risk Sharing Arrangement (RSA) (paragraphs 1.2 and 5.1, romosozumab PSD, March 2024).

For more detail on PBAC's view, see section 7 PBAC outcome.

3 Requested listing

3.1 The requested listings proposed in the submission are detailed below.

Requested listing – initiating in patients with severe established osteoporosis with very high risk of fracture

Name, restriction, manner of administration and form	Treatment phase	Max Quantity (packs)	Max Quantity (units)	Number of repeats	DPMQ	Proprietary name and manufacturer
Abaloparatide, severe established osteoporosis, 2 mg/mL injection, 1.5 mL pre-filled pen	Initial – first-line therapy	1	1	5	$[redacted]	Eladynos – Theramex Australia Pty Ltd.
Category / Program: General (GE)						
Prescriber type: ☐Dental ☒Medical Practitioners ☐Nurse practitioners ☐Optometrists ☐Midwives						
Restriction type: ☐Restricted benefit ☐Authority Required – In writing ☐Authority Required (STREAMLINED) ☒Authority Required (telephone/electronic)						
Condition: Severe established osteoporosis						
PBS indication: severe established osteoporosis						
Treatment Phase: initial treatment (first-line therapy)						
Clinical criteria: Patient must not have received PBS-subsidised treatment with any of: (i) anti-resorptive therapy, (ii) teriparatide, or (iii) romosozumab, or (iv) abaloparatide, OR Patient must have developed intolerance to antiresorptive treatments or romosozumab of a severity necessitating permanent treatment withdrawal within the first 6 months of therapy. AND Patient must be at very high risk of fracture, AND Patient must have a Bone Mineral Density (BMD) T-score of -2.5 or less, AND Patient must have had a symptomatic fracture due to minimal trauma, AND Patient must have had at least 1 hip or symptomatic vertebral fracture in the previous 24 months; OR Patient must have had at least 2 fractures including 1 symptomatic new fracture in the previous 24 months, AND The treatment must be the sole PBS-subsidised therapy for this condition, AND The treatment must not exceed a lifetime maximum of 18 months of PBS and non-PBS-subsidised therapy.						
Treatment criteria: Must be treated by a consultant physician,						
Population criteria: Patient must be aged 18 years or older						
Prescriber instructions: • Details of fracture history including the date(s), site(s), the symptoms associated with the fracture(s) and the score of the qualifying BMD measurement must be provided at the time of application. • A vertebral fracture is defined as a 20% or greater reduction in height of the anterior or mid portion of a vertebral body relative to the posterior height of that body, or a 20% or greater reduction in any of these heights compared to the vertebral body above or below the affected vertebral body. • Anti-resorptive therapies for osteoporosis include alendronate sodium, risedronate sodium, raloxifene hydrochloride, denosumab and zoledronic acid.						

Requested listing – continuing in patients with severe established osteoporosis with very high risk of fracture

Name, restriction, manner of administration and form	Treatment phase	Max Quantity (packs)	Max Quantity (units)	Number of repeats	DPMQ	Proprietary name and manufacturer
Abaloparatide, severe established osteoporosis, 2 mg/mL injection, 1.5 mL pre-filled pen	Continuing – first-line therapy	1	1	5	$[redacted]	Eladynos – Theramex Australia Pty Ltd.
Category / Program: General (GE)						
Prescriber type: ☐Dental ☒Medical Practitioners ☐Nurse practitioners ☐Optometrists ☐Midwives						
Restriction type: ☐Restricted benefit ☐Authority Required – In writing ☐Authority Required (STREAMLINED) ☒Authority Required (telephone/electronic)						
Condition: Severe established osteoporosis						
PBS indication: severe established osteoporosis						
Treatment Phase: continuing treatment (first-line therapy)						
Clinical criteria: Patient must have previously received PBS-subsidised treatment with this drug for this condition as first-line therapy, AND The treatment must be the sole PBS-subsidised therapy for this condition, AND The treatment must not exceed a lifetime maximum of 18 months of PBS and non-PBS-subsidised therapy.						
Treatment criteria: Must be treated by a medical practitioner identifying as either: (i) a consultant physician, (ii) a general practitioner						
Population criteria: Patient must be aged 18 years or older						
Prescriber instructions: • Details of fracture history including the date(s), site(s), the symptoms associated with the fracture(s) and the score of the qualifying BMD measurement must be provided at the time of application. • A vertebral fracture is defined as a 20% or greater reduction in height of the anterior or mid portion of a vertebral body relative to the posterior height of that body, or, a 20% or greater reduction in any of these heights compared to the vertebral body above or below the affected vertebral body. • Anti-resorptive therapies for osteoporosis include alendronate sodium, risedronate sodium, raloxifene hydrochloride, denosumab and zoledronic acid.						

3.2 The submission proposed to list abaloparatide on the General Schedule for patients with severe established osteoporosis and very high risk of fracture. The request for a gender agnostic listing aligned with the current PBS restriction for romosozumab in the first line setting. However, abaloparatide is currently TGA approved for use in postmenopausal women with increased risk of fracture, but not in premenopausal women, or in men, whereas romosozumab has been TGA approved for use in both men and postmenopausal women with osteoporosis at high risk of fracture. (A comparison of abaloparatide and romosozumab in men was provided in the submission. Both abaloparatide and romosozumab provided statistically significantly greater improvement from baseline BMD scores versus placebo). The Pre-Sub Committee Response (PSCR) stated that a TGA indication in men was not possible

because results from the clinical trial conducted in men (ATOM) were not available at the time of TGA registration. The ESC considered that if abaloparatide is PBS listed for osteoporosis, a gender agnostic listing may be appropriate to counter potential under-treatment of osteoporosis in men due to access restrictions.

3.3 The requested restriction would position abaloparatide as first-line therapy according to the criterion: "Patient must not have received PBS-subsidised treatment with any of: (i) anti-resorptive therapy, (ii) teriparatide, or (iii) romosozumab, or (iv) abaloparatide". This is narrower than the approved TGA indication, which is for "osteoporosis in postmenopausal women at increased risk of fracture." The evaluation noted that restricting PBS-subsidised access to patients who have not had prior ART may incentivise clinicians to prescribe abaloparatide as a first line treatment and hence replace some use of ART. The PSCR stated that the requested listing reflects patients enrolled in the key abaloparatide study (ACTIVE) and that there is no RCT evidence supporting the use of abaloparatide in the second-line setting. However, the ESC considered that restricting abaloparatide to first-line use would not be reasonable. With reference to patients who have received prior therapy with teriparatide or romosozumab, the ESC noted that anabolic treatments for osteoporosis are limited to once per lifetime.

3.4 The proposed restriction would allow switching between therapies due to intolerance.

- Patients withdrawing from therapy due to severe intolerance within the first 6 months of the therapy would be eligible to switch to abaloparatide, according to the criterion "Patient must have developed intolerance to anti-resorptive treatments or romosozumab of a severity necessitating permanent treatment withdrawal within the first 6 months of therapy".
- Patients who develop severe intolerance, but withdraw from the therapy after the first 6 months of treatment, will not be eligible for abaloparatide. This criterion was not reflected in the abaloparatide trial in the submission (ACTIVE trial).

For more detail on PBAC's view, see section 7 PBAC outcome.

4 Population and disease

4.1 Osteoporosis is a common and progressive bone disorder characterised by loss of bone mass, resulting in skeletal fragility and increased risk of fracture. Women are at higher risk for osteoporosis than men[1]. In post-menopausal women, estrogen deficiency leads to increased osteoclast differentiation and activation, accelerated

[1] Keen M, Reddivari A. Osteoporosis in Females. StatPearls [Internet]. June 12, 2023. Available at: Osteoporosis in Females - StatPearls - NCBI Bookshelf

bone resorption, and bone loss[2]. In men, hypogonadism, glucocorticoid therapy, gastrointestinal disease, vitamin D deficiency, anticonvulsant medications, hypercalciuria, and alcohol abuse are the most common causes of osteoporosis[3]. In Australia, around 853,600 (3.4%) people were estimated to be living with osteoporosis or osteopenia (decreased bone density) in 2022[4]. Evidence has suggested that osteoporosis is underdiagnosed and undertreated in Australia[5], particularly in men[6].

4.2 Vertebral fractures are the most common osteoporotic fractures. They are associated with an 8-fold increase in age-adjusted mortality and symptoms such as back pain, loss of height, spine deformity, immobility, increased number of bed days, and reduced pulmonary function in those with thoracic kyphosis[7]. Hip fractures are associated with the highest morbidity and mortality among all osteoporosis-associated clinical fractures, with mortality rates up to 20-24% in the first year after a hip fracture. Evidence suggests that mortality in men after a hip fracture is consistently higher than in women[8]. Hip fractures can also result in profound loss of function and loss of independence among survivors[8]. There is an 86% increased risk of a subsequent fracture following an initial osteoporotic fracture, with the highest risk of a subsequent fracture occurring within the first two years after an initial fracture[6].

4.3 A diagnosis of osteoporosis is based on:

1) the measurement of bone mineral density (BMD) of the lumbar spine and femoral neck, using the dual-energy X-ray absorptiometry (DXA) scan. A resulting T-score (the level of BMD in comparison to a young adult of the same gender with peak BMD) ≤ -2.5 is consistent with the diagnosis of osteoporosis, even though a fragility fracture has not occurred, or

[2] Walker MD & Shane E. Postmenopausal osteoporosis. New England Journal of Medicine. 2023; 389(21): 1979-1991.

[3] Kelepouris N, Harper KD, Gannon F et al. Severe osteoporosis in men. Annals of Internal Medicine. 1995; 123(6): 452-460.

[4] AIHW. Chronic musculoskeletal conditions: Osteoporosis and minimal trauma fractures. URL: https://www.aihw.gov.au/reports/chronic-musculoskeletal-conditions/osteoporosis

[5] Naik-Panvelkar P, Normal S, Elgebaly Z et al. Osteoporosis management in Australian general practice: an analysis of current osteoporosis treatment patterns and gaps in practice. BMC Family Practice. 2020; 21(1): 32.

[6] Rinonapoli G, Ruggiero C, Meccariello L. Osteoporosis in men: a review of an underestimated bone condition. International Journal of Molecular Sciences. 2021; 22(4): 10.3390/ijms22042105.

[7] International Osteoporosis Foundation. Epidemiology of osteoporosis and fragility fractures. 2025. URL: https://www.osteoporosis.foundation/facts-statistics/epidemiology-of-osteoporosis-and-fragility-fractures#ref_bottom_2

[8] Trombetti A, Herrmann F, Hoffmeyer P et al. Survival and potential years of life lost after hip fracture in men and age-matched women. Osteoporosis International. 2002; 13(9): 731-737.

2) the presence of a fragility fracture, particularly at the spine, hip, wrist, humerus, rib, or pelvis, regardless of BMD[9].

4.4 The Fracture Risk Assessment Tool (FRAX®)[10] is a computer-based algorithm which utilises clinical risk factors for fracture, including (1) age, (2) previous fracture, (3) glucocorticoid therapy, (4) parental history of hip fracture, (5) low body weight, (6) current cigarette smoking, (7) excessive alcohol consumption, (8) rheumatoid arthritis, and (9) secondary osteoporosis (e.g., hypogonadism or premature menopause, malabsorption, chronic liver disease, inflammatory bowel disease), as well as the femoral neck BMD (g/cm^2, using DXA), when available, to estimate a 10-year probability of hip and major osteoporotic fracture (hip, clinical spine, proximal humerus, or forearm) in untreated osteoporotic patients. Currently, The Royal Australian College of General Practitioners (RACGP) in their March 2024 Guideline recommend either the Garvan Fracture Risk Calculator tool[11] or FRAX® for assessing fracture risk for a treatment decision.

4.5 Individuals with a BMD T-score ≤-3.0, as well as risk factors including concurrent glucocorticoid therapy, low body mass index (BMI), recent acute weight loss, and recurrent falls, are at increased risk of fracture[12]. The most commonly used criteria for "very high fracture risk" in osteoporotic patients are a recent fracture (within 12 or 24 months), multiple fractures, fractures while on therapy, and a 10-year FRAX® major osteoporotic fracture risk of ≥30% or a hip fracture risk of >4.5%[11].

4.6 Abaloparatide is an agonist of the parathyroid hormone receptor 1 (PTHR1). It stimulates new bone formation on trabecular and cortical bone surfaces by stimulation of osteoblastic activity. Abaloparatide causes transient and limited increases in bone resorption and increases bone density[13]. The proposed dosage of abaloparatide was 80 micrograms subcutaneous (SC) self-injection once daily via a pre-fill pen device. The proposed maximum total duration of abaloparatide treatment was 18 months. Patients receiving abaloparatide are recommended to receive supplemental calcium and vitamin D if dietary intake of these is inadequate. As per the approved abaloparatide production information (PI), following cessation of the

[9] Rosen HN & Drake MT. Clinical manifestation, diagnosis, and evaluation of osteoporosis in postmenopausal women. UpToDate. URL: https://www.uptodate.com/contents/clinical-manifestations-diagnosis-and-evaluation-of-osteoporosis-in-postmenopausal-women?sectionName=DIAGNOSIS&topicRef= 145467& anchor= H6&source=bqp#H6

[10] FRAX® Fracture Risk Assessment Tool. URL: https://fraxplus.org/

[11] Garvan Institute of Medical Research. Bone Fracture Risk Calculator. URL: https://www.garvan.org.au/research/bone-fracture-risk-calculator

[12] RACGP. Guideline - Osteoporosis management and fracture prevention in post-menopausal women and men > 50 years of age. URL: https://www.racgp.org.au/clinical-resources/clinical-guidelines/key-racgp-guidelines/view-all-racgp-guidelines/osteoporosis/risk-factors/assessment-of-absolute-fracture-risk

[13] Hattersley G, Dean T, Corbin BA et al. Binding selectivity of abaloparatide for PTH-type-1-receptor conformations and effects on downstream signalling. Endocrinology. 2016; 157(1): 141-149.

therapy, patients may be continued on an ART (e.g. bisphosphonates) for ongoing treatment of osteoporosis. Following anabolic treatment, subsequent treatment with an ART helps to consolidate gains in bone density and further reduce fracture risk[14].

4.7 In the approved abaloparatide PI, there is a special warning about the long-term use of abaloparatide and its association with the risk of osteosarcoma, based on study results in rats. Given this, the maximum total duration of abaloparatide therapy is recommended to be 18 months in a lifetime. There are also special warnings on the drug's association with orthostatic hypotension, increased heart rate, hypercalcaemia, hypercalciuria/urolithiasis, as well as the precautions for use in patients with renal and hepatic impairment. Patients with certain conditions, including hypersensitivity to the drug, pregnancy, breastfeeding, childbearing potential, pre-existing hypercalcaemia, severe renal impairment, unexplained elevations of serum alkaline phosphatase, known risks for osteosarcoma (e.g. those who have received prior external beam or implant radiation therapy involving the skeleton), and skeletal malignancies or bone metastases, are contraindicated to abaloparatide treatment.

For more detail on PBAC's view, see section 7 PBAC outcome.

5 Comparator

5.1 Romosozumab was nominated as the primary comparator in the submission. The RACGP guideline (March 2024) recommends romosozumab as the first-line pharmacotherapy for osteoporotic men and post-menopausal women with very high risk of fracture. Duration of treatment is 12 months. After completing romosozumab therapy, continued therapy for osteoporosis with an ART is recommended.

5.2 As per the approved romosozumab PI, the drug is contraindicated in patients with previous myocardial infarction (MI) or stroke. There is special warning in the romosozumab PI about an increase in serious cardiovascular events (MI and stroke) observed in romosozumab treated patients in randomised controlled studies compared to controls. In the section of "Special warnings and precautions for use" in the romosozumab PI, it is stated that, "When determining whether to use romosozumab for an individual patient, consideration should be given to their fracture risk over the next year and their cardiovascular risk based on risk factors (e.g. established cardiovascular disease, hypertension, hyperlipidaemia, diabetes mellitus, smoking, severe renal impairment, age). Romosozumab should only be used if the prescriber and patient agree that the benefit outweighs the risk."

5.3 The PBAC noted that romosozumab is PBS-listed for first-line and second-line use for patients with severe established osteoporosis. The PBAC agreed with the evaluation

[14] Kim A and Girgis C. Anabolic therapy: a new paradigm for osteoporosis management. Endocrinology Today 2021: 10(4):20-25.

that romosozumab is an appropriate comparator for patients who do not have a history of MI or stroke and those in whom the clinician considers romosozumab treatment will outweigh their risk for developing these serious cardiovascular events. However, for patients who are contraindicated to romosozumab or with risk factors that the safety of romosozumab treatment is of concern, romosozumab may not be an appropriate comparator. For this particular population, ARTs may be the appropriate comparator. However, no comparative evidence regarding the efficacy and safety of abaloparatide versus ART was presented in the submission. The size of this population is uncertain.

5.4 Teriparatide, which has the same mechanism of action as abaloparatide, is PBS listed as a second-line treatment following ART. The proposed restriction excludes second-line treatment with abaloparatide, and hence the submission did not consider teriparatide as a comparator. The evaluation noted that teriparatide was a comparator to abaloparatide in the randomised controlled trial, ACTIVE, for the secondary outcomes of BMD and for safety. The PBAC considered that teriparatide should be considered a relevant comparator for second-line use.

For more detail on PBAC's view, see section 7 PBAC outcome.

6 Consideration of the evidence

Sponsor hearing

6.1 The sponsor requested a hearing for this item. The clinician described the global change in approach to treatment in bone fragility in terms of rebuilding bone with anabolic treatment followed by ART to maintain BMD. The clinician discussed the small risk of increase in CV events (stroke and myocardial infarction) with romosozumab, noting that it is not suitable for all patients and the benefit of having another treatment option with abaloparatide. The PBAC considered that the hearing was informative, as it provided a clinical perspective on the place in therapy for abaloparatide and the clinical need for an alternative agent.

Consumer comments

6.2 The PBAC noted and welcomed the input from eight health care professionals (HCPs) and Healthy Bones Australia via the Consumer Comments facility on the PBS website.

6.3 Healthy Bones Australia indicated its support for the application for abaloparatide as a first-line treatment in Australia. It emphasised the increasing evidence to suggest that anabolic agents should be used first-line to build new bone, followed by ART to preserve new bone. The organisation noted the effective clinical trial evidence for abaloparatide versus placebo and noted the absence of adverse cardiovascular events associated with abaloparatide.

6.4 The HCPs commented that abaloparatide is an effective treatment for patients with severe osteoporosis as described by the following points: it is a potent anabolic agent which allows for bone formation and improvement of bone density and quality; it has demonstrated clinical trial evidence for efficacy improving bone density and strength, and reducing fracture risk; and it is easily administered as a daily injection without requirement to refrigerate. The HCPs also commented that the cardiovascular contraindications to the PBS-listed anabolic treatment, romosozumab, may leave many individuals without access to first-line anabolic treatment.

Clinical trials

6.5 No head-to-head trials were identified that directly compared abaloparatide vs romosozumab in the proposed PBS target population (men and women with severe established osteoporosis and very high risk of fracture who have not received prior treatment). Therefore, the submission was based on:

- one randomised controlled trial (RCT) (ACTIVE) which compared abaloparatide to placebo and teriparatide in postmenopausal women with osteoporosis;
- one RCT (FRAME) that compared romosozumab to placebo in postmenopausal women with osteoporosis.

The trials were indirectly compared using placebo as the common reference. The indirect treatment comparison (ITC) between abaloparatide and romosozumab assessed their respective efficacy in reducing new vertebral fractures, nonvertebral fractures, and clinical fractures. The extension studies of the trials also informed an ITC between these two drugs regarding their residual effectiveness in preventing new vertebral fractures, nonvertebral fractures, and clinical fractures.

6.6 The submission also presented efficacy and safety data in osteoporotic men. The ATOM trial compared abaloparatide to placebo and the BRIDGE trial compared romosozumab to placebo. The results from these trials were not presented by the evaluation, as abaloparatide was not TGA approved for use in men at the time of evaluation.

6.7 Details of the key trials presented in the submission are provided in Table 2.

Table 2: Trials and associated reports presented in the submission

Trial ID	Protocol title/ Publication title	Publication citation
Abaloparatide trials		
ACTIVE NCT01343004	Radius Health Inc (2015). BA058-05-003: A Randomized, Double-blind, Placebo-controlled, Comparative Phase 3 Multicenter Study to Evaluate the Safety and Efficacy of BA058 for Injection for Prevention of Fracture in Ambulatory Postmenopausal Women with Severe Osteoporosis and at Risk of Fracture. Clinical Study Report	
	Radius Health Inc. (2011). NCT01343004: A Randomized, Double-blind, Placebo-Controlled, Comparative Multicenter Phase 3 Study to Evaluate the Safety and Efficacy of BA058 (Abaloparatide) for Injection for Prevention of Fracture in Ambulatory Postmenopausal Women With Severe Osteoporosis and at Risk of Fracture.	
	Miller PD, Hattersley G, Riis BJ, et al. Effect of abaloparatide vs placebo on new vertebral fractures in postmenopausal women with osteoporosis: a randomized clinical trial.	JAMA 2016; 316(7): 722-733.
	Bilezikian, JP, Hattersley G, Mitlak BH, et al. Abaloparatide in patients with mild or moderate renal impairment: results from the ACTIVE phase 3 trial.	Current Medical Research and Opinion 2019; 35(12): 2097-2102.
	Cosman, F, Hattersley G, Hu MY, et al. Effects of abaloparatide-SC on fractures and bone mineral density in subgroups of postmenopausal women with osteoporosis and varying baseline risk factors.	Journal of Bone and Mineral Research 2017; 32(1): 17-23.
	Cosman, F, Peterson LR, Towler DA, et al. Cardiovascular safety of abaloparatide in postmenopausal women with osteoporosis: analysis from the active phase 3 trial.	Journal of Clinical Endocrinology and Metabolism 2020;105(11): 1-12.
	DeSapri, KT, Clarke BL, Kostenuik P, et al. Effect of abaloparatide on fracture incidence and bone mineral density in postmenopausal women with osteoporosis at highest risk for fracture.	Menopause 2025
	Dhaliwal, R, Hans D, Hattersley G, et al. Abaloparatide in postmenopausal women with osteoporosis and type 2 diabetes: a post hoc analysis of the active study.	JBMR Plus 2020; 4(4) (no pagination).
	Leder, BZ, Mitlak B, Hu MY, et al. Effect of abaloparatide vs alendronate on fracture risk reduction in postmenopausal women with osteoporosis.	Journal of Clinical Endocrinology and Metabolism 2020; 105(3) (no pagination).
	McCloskey, EV, Fitzpatrick LA, Hu MY, et al. Effect of abaloparatide on vertebral, nonvertebral, major osteoporotic, and clinical fractures in a subset of postmenopausal women at increased risk of fracture by FRAX probability.	Archives of Osteoporosis 2019; 14(1): 15.
	McCloskey, EV, Johansson H, Oden A, et al. The Effect of Abaloparatide-SC on Fracture Risk Is Independent of Baseline FRAX Fracture Probability: A Post Hoc Analysis of the ACTIVE Study.	Journal of Bone & Mineral Research 2017; 32(8): 1625-1631.
	McClung, MR, Harvey NC, Fitzpatrick LA, et al. Effects of abaloparatide on bone mineral density and risk of fracture in postmenopausal women aged 80 years or older with osteoporosis.	Menopause 2018; 25(7): 767-771.
	McClung, MR, Williams GC, Hattersley G, et al. Geography of fracture	Calcified Tissue International

Trial ID	Protocol title/ Publication title	Publication citation
	incidence in postmenopausal women with osteoporosis treated with abaloparatide.	2018; 102(6): 627-633.
	Miller, PD, Hattersley G, Lau E, et al. Bone mineral density response rates are greater in patients treated with abaloparatide compared with those treated with placebo or teriparatide: Results from the ACTIVE phase 3 trial.	Bone 2019; 120: 137-140.
	Moreira, CA, Fitzpatrick LA, Wang Y, et al. Effects of abaloparatide-SC (BA058) on bone histology and histomorphometry: The ACTIVE phase 3 trial."	Bone 2017; 97: 314-319.
	Reginster, JY, Hattersley G, Williams GC, et al. Abaloparatide is an effective treatment option for postmenopausal osteoporosis: Review of the number needed to treat compared with teriparatide.	Calcified Tissue International 2018; 103(5): 540-545.
	Saag, KG, Williams SA, Wang Y, et al. Effect of abaloparatide on bone mineral density and fracture incidence in a subset of younger postmenopausal women with osteoporosis at high risk for fracture.	Clinical Therapeutics 2020; 42(6): 1099-1107.e1091.
	Watts, NB, Hattersley G, Fitzpatrick LA, et al. Abaloparatide effect on forearm bone mineral density and wrist fracture risk in postmenopausal women with osteoporosis.	Osteoporosis International 2019; 30(6): 1187-1194.
ACTIVExtend NCT01657162	Radius Health Inc (2017). BA058-05-005: An extension study to evaluate 24 months of standard-of-care osteoporosis management following completion of 18 months of ba058 or placebo treatment in protocol ba058-05-003. Clinical Study Report	
	Radius Health Inc. (2012). NCT01657162: An extension study to evaluate 24 months of standard-of-care osteoporosis management following completion of 18 months of ba058 or placebo treatment in protocol ba058-05-003	
	Bone, HG, Cosman F, Miller PD, et al. ACTIVExtend: 24 months of alendronate after 18 months of abaloparatide or placebo for postmenopausal osteoporosis.	Journal of Clinical Endocrinology & Metabolism 2018; 103(8): 2949-2957.
	Cosman, F, Miller PD, Williams GC, et al. Eighteen months of treatment with subcutaneous abaloparatide followed by 6 months of treatment with alendronate in postmenopausal women with osteoporosis: results of the ACTIVExtend trial.	Mayo Clinic Proceedings 2017; 92(2): 200-210.
	Leder, BZ, Zapalowski C, Hu MY, et al. Fracture and bone mineral density response by baseline risk in patients treated with abaloparatide followed by alendronate: results from the phase 3 ACTIVExtend trial.	Journal of Bone and Mineral Research 2019; 34(12): 2213-2219.
ATOM (abaloparatide study in men) NCT03512262	Radius Health Inc. (2018). NCT03512262: A Randomized, Double-blind, Placebo-controlled, Phase 3 Multicenter Study to Evaluate the Safety and Efficacy of Abaloparatide-SC for the Treatment of Men With Osteoporosis.	
	Dhaliwal, R, Kendler D, Saag K, et al. Response rates for lumbar spine, total hip, and femoral neck bone mineral density in men treated with abaloparatide: results from the ATOM study.	JBMR Plus 2024; 8(2) (no pagination).
	Eastell, R, Brown JP, Adler RA, et al. Bone turnover markers predict changes in bone mineral density in men treated with abaloparatide: results from ATOM.	Journal of Bone & Mineral Research 2025; 10.

Trial ID	Protocol title/ Publication title	Publication citation
Abaloparatide RWE		
NCT04974723	Tabatabai, L, Cosman F, Curtis JR, et al. Comparative effectiveness of abaloparatide and teriparatide in women 50 years of age and older: update of a real-world retrospective analysis.	Endocrine Practice 2025; 31(2): 159-168.
	Radius Health Inc (2021). BA058-05-028: A retrospective, observational cohort study evaluating the effectiveness and cardiovascular safety of abaloparatide in postmenopausal women new to anabolic therapies. Clinical Study Report	
	Cosman, F, Cooper C, Wang Y, et al. Comparative effectiveness and cardiovascular safety of abaloparatide and teriparatide in postmenopausal women new to anabolic therapy: A US administrative claims database study.	Osteoporos Int 2022; 33(8): 1703-1714.
	Radius Health Inc (2021): A Retrospective, Observational Cohort Study Evaluating the Effectiveness and Cardiovascular Safety of Abaloparatide in Postmenopausal Women New to Anabolic Therapies.	
Romosozumab trials		
FRAME NCT01575834	Cosman, F, Crittenden DB, Adachi JD, et al. Romosozumab treatment in postmenopausal women with osteoporosis.	New England Journal of Medicine 2016; 375(16): 1532-1543.
	Cosman, F, Cooper C, Wang Y, et al. Comparative effectiveness and cardiovascular safety of abaloparatide and teriparatide in postmenopausal women new to anabolic therapy: A US administrative claims database study.	Osteoporos Int 2022; 33(8): 1703-1714.
	Chavassieux, P, Chapurlat R, Portero-Muzy N, et al. Bone-forming and antiresorptive effects of romosozumab in postmenopausal women with osteoporosis: bone histomorphometry and microcomputed tomography analysis after 2 and 12 months of treatment.	Journal of Bone and Mineral Research 2019; 34(9): 1597-1608.
	Cosman, F, Crittenden DB, Ferrari S, et al. Romosozumab FRAME study: a post hoc analysis of the role of regional background fracture risk on nonvertebral fracture outcome.	Journal of Bone and Mineral Research 2018; 33(8): 1407-1416.
	Langdahl, B, Hofbauer LC, Ferrari S, et al. Romosozumab efficacy and safety in European patients enrolled in the FRAME trial.	Osteoporosis International 2022; 33(12): 2527-2536.
	McCloskey, EV, Johansson H, Harvey NC, et al. Romosozumab efficacy on fracture outcomes is greater in patients at high baseline fracture risk: a post hoc analysis of the first year of the frame study.	Osteoporosis International 2021; 32(8): 1601-1608.
	Miller, PD, Adachi JD, Albergaria BH, et al. Efficacy and safety of romosozumab among postmenopausal women with osteoporosis and mild-to-moderate chronic kidney disease.	Journal of Bone & Mineral Research 2022; 37(8): 1437-1445.
	Miyauchi, A, Dinavahi RV, Crittenden DB, et al. Increased bone mineral density for 1 year of romosozumab, vs placebo, followed by 2 years of denosumab in the Japanese subgroup of the pivotal FRAME trial and extension.	Archives of Osteoporosis. 2019; s14(1) (no pagination).
	Miyauchi, A, Hamaya E, Yang W, et al. Romosozumab followed by denosumab in Japanese women with high fracture risk in the FRAME trial.	Journal of Bone and Mineral Metabolism 2021; 39(2): 278-288.

Trial ID	Protocol title/ Publication title	Publication citation
	Cosman, F, Crittenden DB, Ferrari S, et al. FRAME Study: the foundation effect of building bone with 1 year of romosozumab leads to continued lower fracture risk after transition to denosumab.	Journal of Bone and Mineral Research 2018; 33(7): 1219-1226.
	Lewiecki, EM, Dinavahi RV, Lazaretti-Castro M, et al. One year of romosozumab followed by two years of denosumab maintains fracture risk reductions: results of the frame extension study.	Journal of Bone and Mineral Research 2019; 34(3): 419-428.
	Cosman, F, Oates M, Betah D, et al. Romosozumab followed by denosumab vs. denosumab only: a post hoc analysis of FRAME and FRAME extension.	Journal of Bone & Mineral Research 2024; 39(9): 1268-1277.
	Geusens, P, Feldman R, Oates M, et al. Romosozumab reduces incidence of new vertebral fractures across severity grades among postmenopausal women with osteoporosis.	Bone 2022;154 (no pagination)
BRIDGE (romosozumab study in men) NCT02186171	Lewiecki, EM, Blicharski T, Goemaere S, *et al.* A phase III randomized placebo-controlled trial to evaluate efficacy and safety of romosozumab in men with osteoporosis.	The Journal of Clinical Endocrinology & Metabolism 2018; 103(9): 3183-3193.
	Amgen (2014). NCT02186171: A multicenter, randomized, double-blind, placebo-controlled study to compare the efficacy and safety of romosozumab with placebo in men with osteoporosis.	

Source: Table 2-5, pp40-45 of the submission
RWE = real world evidence

6.8 The key features of the included evidence in postmenopausal women for the indirect comparison are summarised in Table 3.

Table 3: Key features of the included evidence for postmenopausal women (main studies and extension studies)

Trial	N	Design/ duration	Risk of bias	Patient population	Outcome(s)
Abaloparatide vs placebo					
ACTIVE	2,070[a]	R, MC, DB 18 mths	Low	Postmenopausal women with osteoporosis	• Incidence of new vertebral fractures [d] • Risk of nonvertebral fracture and clinical fractures
Abaloparatide vs placebo (extension study using subsequent open label alendronate)					
ACTIVExtend	963[b]	MC, OL[c], 24 mths		Postmenopausal women with osteoporosis	• Incidence of new vertebral fractures [e] • Risk of nonvertebral fracture and clinical fractures
Romosozumab vs placebo					
FRAME	7,180	R, MC, DB 12 mths	Low	Postmenopausal women with osteoporosis	• Incidence of new vertebral fractures • Risk of nonvertebral fracture and clinical fractures
Romosozumab vs placebo (extension study using subsequent open label denosumab)					
FRAME extension study	6,390	MC, OL [c] 24 mths		Postmenopausal women with osteoporosis	• Incidence of new vertebral fractures • Risk of nonvertebral fracture and clinical fractures

Source: Compiled during the evaluation based on information provided in Section 2.2-2.3 of the submission
DB = double blind; ITT = intention-to-treat; MC = multi-centre; OL = open-label; R = randomised
[a] The ITT excluding 652 patients from two non-Good Clinical Practice study sites by the request of the Committee on Human Medicinal Products.
[b] Excluding patients from the two non-Good Clinical Practice study sites.
[c] Patients received open-label alendronate in ACTIVExtend (or open-label denosumab in FRAME extension study). However, patients and investigators were still blinded to the previous allocated treatment (abaloparatide or romosozumab).
[d] Only patients who had the pre-treatment and the post-baseline evaluable radiologic assessment, i.e., the modified ITT (N = 1783) were included for the analysis of this outcome.
[e] Includes all ACTIVE modified ITT patients who had a ACTIVExtend post baseline evaluable radiologic assessment (spine x-ray).

6.9 The ACTIVE study was a Phase 3, multi-centre RCT comparing abaloparatide 80 micrograms subcutaneous (SC) injection once daily with placebo and with teriparatide 20 micrograms in postmenopausal women with osteoporosis for an 18-month treatment period. In ACTIVE, originally 2,463 patients were randomised to one of the three treatments. Patients randomised to the abaloparatide, and placebo arms received double-blind allocated treatment. Patients randomised to the teriparatide arm received open-label teriparatide treatment. By the request of the Committee on Human Medicinal Products (CHMP), patients from two study sites in ACTIVE were removed from outcome analyses due to Good Clinical Practice (GCP) related issues. As a result, 2,070 patients were included in the intention-to-treat (ITT) population, with 696 patients in the abaloparatide arm and 688 patients in the placebo arm.

6.10 All patients who were randomised to the abaloparatide and placebo arm (but not the teriparatide arm), and completed 18 months of allocated treatment, were offered the opportunity to participate in the extension phase of the study (ACTIVExtend). In ACTIVExtend, all enrolled patients received open-label oral alendronate 70 mg once per week for 24 months (patients and investigators were blinded to the previous allocated treatment within the first 6 months in ACTIVExtend). There were 963

patients entered into ACTIVExtend, with 469 patients in the abaloparatide/alendronate arm and 494 patients in the placebo/alendronate arm.

6.11 The risk of bias was considered low for ACTIVE and ACTIVExtend for the abaloparatide and placebo arms. The risk of bias for ACTIVE was previously assessed as "unclear" in a romosozumab PSD (Table 4, romosozumab PSD, July 2019) because patients randomised to the teriparatide arm in the study received open-label teriparatide treatment. However, the efficacy outcomes from this study arm were not included in the ITC in the submission.

6.12 The FRAME study was a Phase 3, double-blind, multicentre RCT comparing romosozumab vs placebo in postmenopausal women with osteoporosis. There were 3,589 patients randomised to receive romosozumab and 3,591 to placebo. In FRAME, patients received 12 months of double-blinded, randomised treatment, followed by 24 months of open-label denosumab 60 mg SC every 6 months (patients and investigators were still blinded to the previous allocated treatment) in the FRAME extension study. Risk of bias of FRAME was considered low previously by PBAC (Table 3, romosozumab PSD, November 2018).

6.13 Key differences identified across the ACTIVE and FRAME studies include:

- A higher risk of fracture in ACTIVE compared to FRAME due to differences in history of fracture, risk of further fractures, and BMD T-score:
    - <u>History of fracture</u>

      In ACTIVE, eligible patients had to have radiological evidence of at least two mild or at least one moderate lumbar or thoracic vertebral fracture, or history of low trauma forearm, humerus, sacral, pelvic, hip, femoral, or tibial fracture within the past 5 years. In FRAME, however, there was no such requirement and patients who had a history of hip fracture, any severe or >2 moderate vertebral fractures were excluded from the trial. As a result, comparing the placebo arms in the two trials, 43.9% in ACTIVE had ≥1 previous nonvertebral fracture vs 21.8%[15] in FRAME; and 21.7% of patients in ACTIVE had ≥1 prevalent vertebral fracture at baseline vs 17.9% in FRAME.
    - <u>Study population's risk for further fractures at baseline</u>

      Even though the 10-year FRAX® major osteoporotic fracture risk of the two study populations was similar (13.1% for the ACTIVE population and 13.4% for the FRAME population), ACTIVE may have a study population with a slightly higher risk for further fracture at baseline compared to FRAME. Comparing the outcome of the placebo arms in the two trials at the end of study treatment, there were 25 patients (4.2%) in ACTIVE who had new

[15] Only included fractures occurred at ≥ 45 years of age

vertebral fractures vs 59 patients (1.8%) in FRAME; similarly, there were 21 (3.1%) and 35 (5.1%) in ACTIVE who reported nonvertebral fractures and clinical fractures respectively, compared to 75 (2.1%) and 90 (2.5%) in FRAME.

- Difference in BMD T-score requirement for inclusion

  In ACTIVE, patients with a wider range of BMD T-score (between ≤ -2.5 and > -5.0) were eligible for the trial while FRAME only included patients with a BMD T-score between -2.5 and -3.5.

- **Treatment period**

  The treatment periods in ACTIVE vs FRAME were 18 months vs 12 months, respectively, in line with the treatment period recommended in the Approved PIs for abaloparatide and romosozumab, respectively. It was unclear how the different treatment durations in the two trials have impacted the occurrence of fractures in study patients, given the difference in fracture risk.

- **Treatment sequence**

  In ACTIVExtend, the subsequent treatment after cessation of abaloparatide was alendronate, while in the FRAME extension study, the subsequent treatment was denosumab after romosozumab. The PBAC previously considered that denosumab was associated with a small but statistically significant increase in BMD compared to alendronate (p6, denosumab PSD, July 2010). In a recent retrospective cohort study, Curtis et al[16] demonstrated the efficacy of denosumab (n = 89,115) in reducing the risk of fractures of different categories compared with alendronate (n = 389,536).

- **Definition of clinical fractures**

  In ACTIVE, clinical fractures included all fractures and all levels of trauma causing the fractures. In FRAME, however, clinical fractures included only clinical (symptomatic) vertebral fractures and nonvertebral fractures not associated with severe trauma. Hence, more fractures, particularly nonvertebral fractures associated with severe trauma, may have been reported as clinical fractures in ACTIVE compared to FRAME.

- **Timing and frequency of fracture assessment**

  In ACTIVE, patients received clinical and radiological assessment at Screening and at the end of treatment (Visit 9, Month 18). In ACTIVExtend, patients received clinical and radiological assessment in Month 6 and Month 24 and received clinical

[16] Curtis JR, Arora T, Liu Y et al. Comparative effectiveness of denosumab vs alendronate among postmenopausal women with osteoporosis. Journal of Bone and Mineral Research. 2024; 39(7): 826-834.

assessment of de novo fractures in Month 12 and Month 18. In FRAME, patients received baseline radiological assessment and were then scheduled for reporting nonvertebral and suspected clinical vertebral fracture during the scheduled monthly visits. FRAME patients presenting with symptoms could also receive radiological assessment outside of the scheduled timepoints for assessment. There is the possibility that the incidence of fractures, both vertebral and nonvertebral, was underestimated and underreported in ACTIVE compared to FRAME.

6.14 Overall, the differences in patients' prevalence of vertebral fracture and history of past fractures at baseline, risk for further fractures at baseline, BMD T-score requirements for trial inclusion, treatment period, treatment sequence, definition of the clinical fracture endpoint, and timing and frequency of fracture assessment, all raise concerns about the transitivity of the two trials included in the indirect comparison. Caution should be taken when interpreting the results of the indirect comparison in this context.

Comparative effectiveness

Abaloparatide effectiveness

6.15 Summaries of the primary and key secondary efficacy results of ACTIVE are provided in Table 4, Figure 1, and Figure 2.

Table 4: Summary of the primary and secondary efficacy endpoints of ACTIVE (excluding 2 non-GCP sites)

	Abaloparatide (N = 583[a])	**Placebo (N = 600[a])**
Primary outcome: Incidence of new vertebral fracture		
n (%)	3 (0.51)	25 (4.17)
Risk difference, % (95% CI)	**-3.65 (-5.59, -2.00)**	
Relative risk reduction[b] (95% CI)	**-0.88 (-0.96, -0.59)**	
Risk ratio[c] (95% CI)	**0.12 (0.04, 0.41)**	
p-value[d]	**< 0.0001**	
	Abaloparatide (N = 696[e])	**Placebo (N = 688[e])**
Key secondary outcome: Time to first incidence of nonvertebral fracture[f]		
KM event rate % (95% CI)	2.7 (1.63, 4.44)	3.6 (2.33, 5.42)
Patients with events, n (%)	15 (2.2)	21 (3.1)
Censored patients[g], n (%)	681(97.8)	667 (96.9)
ARR % (95% CI)	–0.87 (–2.89, 1.15)	
HR (95% CI)	0.74 (0.38, 1.43)	
p-value	0.3675	
Key secondary outcome: Time to first incidence of clinical fracture[h]		
KM event rate % (95% CI)	3.8 (2.46, 5.71)	7.4 (4.49, 12.06)
Patients with events, n (%)	21 (3.0)	35 (5.1)
Censored patients, n (%)	675 (97.0)	653 (94.9)
ARR % (95% CI)	–3.64 (–7.63, 0.35)	
HR (95% CI)	0.61 (0.36, 1.06)	
p-value	0.0753	

Source: Table 2-21 & Table 2-24, pp88,94 of the submission; Table 7, Table 9 & Table 10, pp26,31 & 36 of the ACTIVE Clinical Study Report Addendum

ARR = absolute risk reduction; CI = confidence interval; GCP = Good Clinical Practice; HR = hazard ratio; ITT = intention-to-treat; KM = Kaplan Meier; mITT = modified ITT; n = number of patients reporting events.

Figures in bold are statistically significant.

[a] Modified ITT (excluding 2 non-GCP sites) comprised patients in the ITT cohort who had the pre-treatment and the post-baseline evaluable radiologic assessment

[b] Relative risk reduction was calculated as (abaloparatide – placebo) / placebo.

[c] Not reported in the CSR. Value was calculated (using Revman 5.3 calculator) to allow comparison with value reported in FRAME.

[d] p-value was from Fisher's exact test with abaloparatide-SC compared to placebo

[e] ITT population (excluding 2 non-GCP sites)

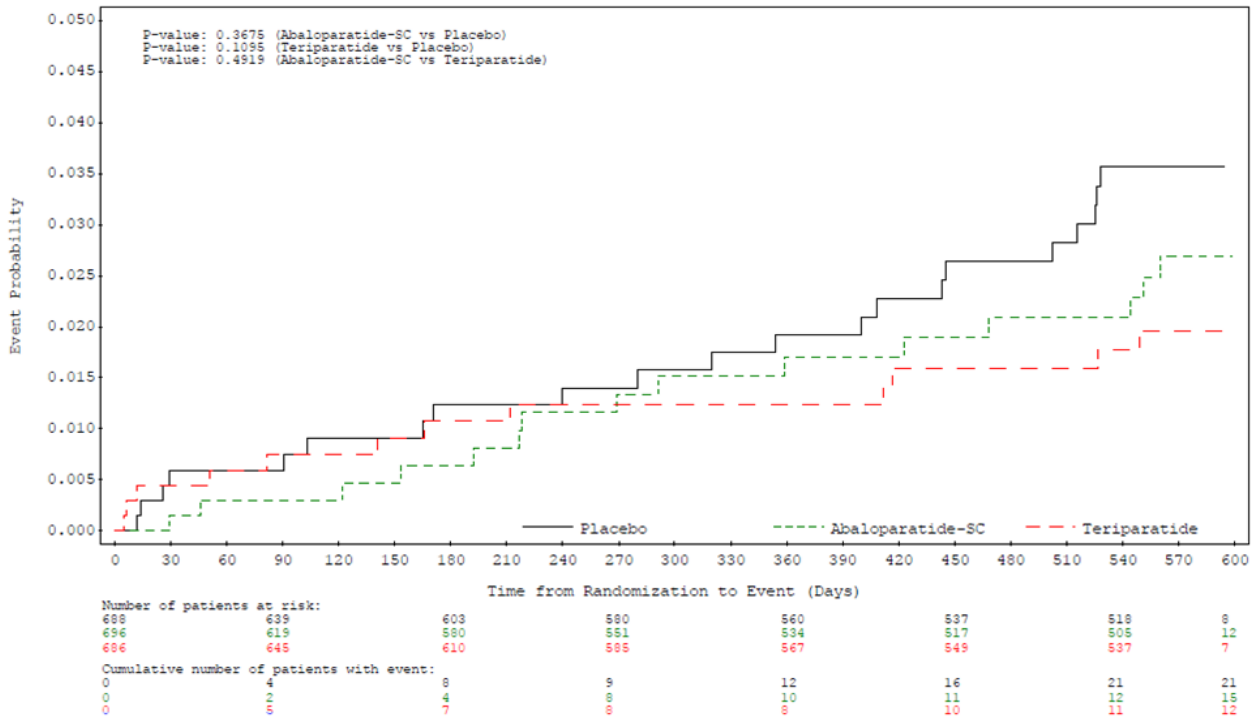
[f] Nonvertebral fractures were clinical fractures[h] that included those of the hip, wrist, forearm, shoulder, collar bone, upper arm, ribs, upper leg (not hip), knee, lower leg (not knee or ankle), foot, ankle, hand, pelvis (not hip), tailbone and other; those associated with low trauma (defined as a fall from standing height or less, or a fall on stairs, steps or curbs); those associated with minimal or moderate trauma other than a fall; but excluded those of the spine, breast bone, knee cap, toes, fingers, skull and facial bones, and pathologic fractures; those associated with high trauma (defined as a fall from a height equal to or higher than the level of "a stool, chair or first rung of a ladder"), and those associated with severe trauma other than a fall.

[g] Duration in days from the randomisation to the first incidence of nonvertebral fracture was derived. If a patient had not experienced any NVF over the 18 months of treatment plus the 30-day follow-up (for a total of 19 months), this patient was considered censored at the last known day in the study up to the Follow-up Visit (Visit 10).

[h] Clinical fractures were all fractures, vertebral and nonvertebral, that would cause a patient to seek medical care, regardless of the level of trauma, including clinical spine.

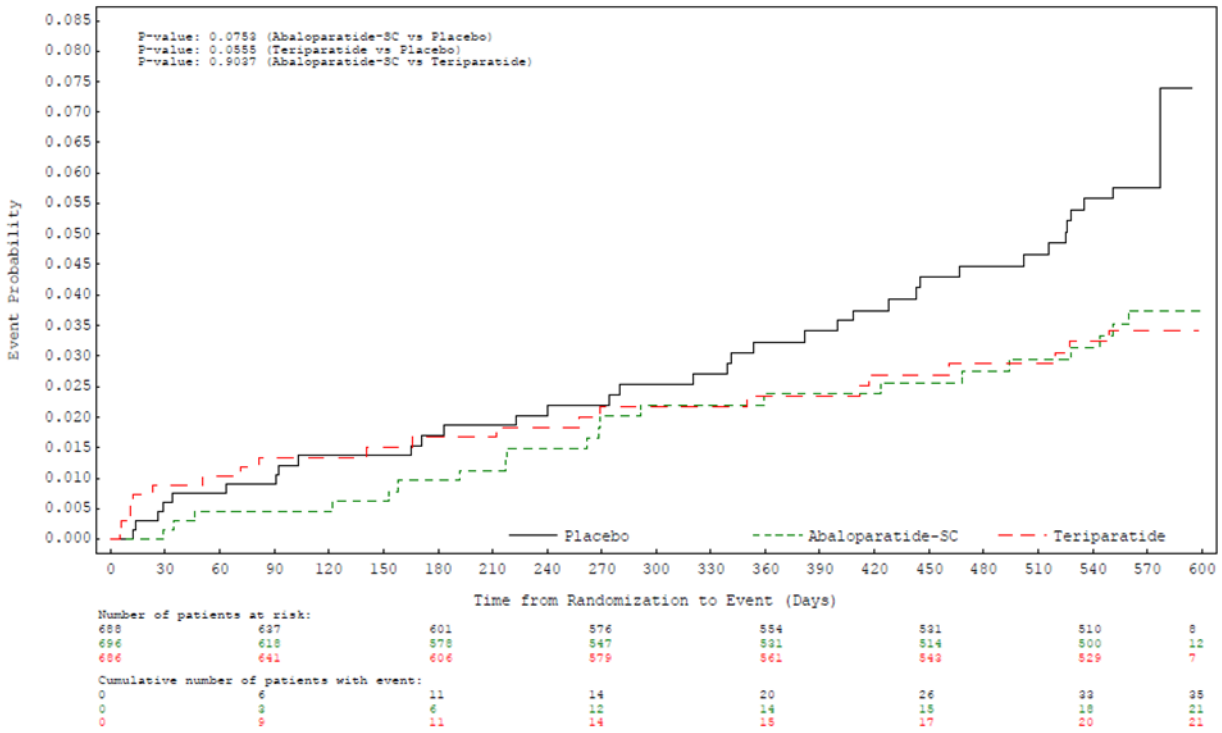
Figure 1: KM curve of time to first incidence of nonvertebral fractures in patients receiving abaloparatide vs placebo for 18 months in ACTIVE[a]

Figure



Source: Figure 2-6, p95 of the submission; Figure 1, p32 of the ACTIVE Clinical Study Report Addendum
GCP = Good Clinical Practice; ITT = intent-to-treat; KM = Kaplan Meier
[a] ITT excluding 2 non-GCP sites

Figure 2: KM curve of time to first incidence of clinical fractures in patients receiving abaloparatide vs placebo for 18 months in ACTIVE[a]



Source: Figure 2-7, p96 of the submission; Figure 3, p39 of the ACTIVE Clinical Study Report Addendum
GCP = Good Clinical Practice; ITT = intent-to-treat; KM = Kaplan Meier
[a] ITT excluding 2 non-GCP sites

6.16 Patients treated with abaloparatide for 18 months demonstrated a statistically significant reduction in the incidence of new vertebral fracture compared to placebo, with an 88% relative risk reduction in new vertebral fracture in patients receiving abaloparatide compared to placebo.

6.17 Abaloparatide treatment prolonged the time to the first incidence of both nonvertebral fracture and clinical fracture compared to placebo, but the hazard ratios (HRs) were not statistically significant for both fracture endpoints. The censoring of a large proportion of treated patients introduced uncertainty into the analyses of these outcomes and impacted the reliability of the results.

6.18 Patients treated with abaloparatide for 18 months followed by alendronate for 24 months in ACTIVExtend demonstrated a statistically significant reduction in the incidence of new vertebral fracture compared to patients receiving placebo followed by alendronate. These results showed that after cessation of abaloparatide therapy for 2 years, abaloparatide-treated patients continued to have a lower risk for new vertebral fracture compared to placebo patients.

6.19 The efficacy of abaloparatide in improving BMD at total hip, femoral neck, and lumbar spine and preventing other fractures was also presented in the submission. However,

these endpoints were not included for the indirect comparison between abaloparatide and romosozumab in the submission.

6.20 In the ACTIVE trial, BMD in abaloparatide patients gained over time at total hip, femoral neck and lumbar spine, while BMD in placebo patients decreased over time at all three anatomical sites. At all the time points, patients treated with abaloparatide had statistically significant percent changes in BMD from baseline at total hip, femoral neck, and lumbar spine compared to placebo. The PBAC previously considered that "the clinical importance of the difference in BMD outcomes was unclear" (paragraph 5.4, romosozumab PSD, November 2018).

Indirect comparison of abaloparatide vs romosozumab

6.21 Anchored indirect comparisons of abaloparatide treatment for 18 months in ACTIVE vs romosozumab for 12 months in FRAME and the residual effectiveness of these two drugs in the extension studies of these two trials, using placebo as the common reference[17], are presented in Table 5 and Table 6.

[17] Bucher HC et al. The results of direct and indirect treatment comparisons in meta-analysis of randomized controlled trials. Journal of Clinical Epidemiology. 1997; 50(6): 683-691.

Table 5: Summary of the results of the ITC comparing the incidence of new vertebral fractures in patients receiving abaloparatide for 18 months followed by alendronate for 24 months vs romosozumab for 12 months followed by denosumab for 24 months

Trial	**ACTIVE (18 months)[a]**		**FRAME (12 months)**	
Treatment/statistics	**Abaloparatide**	**Placebo**	**Romosozumab**	**Placebo**
n/N (%)	3/583 (0.51)	25/600 (4.17)	16/3,321 (0.48)	59/3,322 (1.78)
Risk difference % (95% CI)	**-3.65 (-5.59, -2.00)**		**-1.29 (-1.80, -0.79)**	
ITC risk difference (95% CI, p-value)	**-2.36% (-4.1%, -0.6%), p = 0.009**			
Risk ratio (95% CI)	**0.12 (0.04, 0.41)**		**0.27 (0.16, 0.47)**	
ITC risk ratio (95% CI); p-value	0.46 (0.12, 1.69); p = 0.240			
ITC odds ratio (95% CI); p-value	0.44 (0.12, 1.67); p = 0.230			
	ACTIVExtend		**FRAME extension study**	
Treatment/statistics	**Abaloparatide (18 months) followed by alendronate (24 months)**		**Romosozumab (12 months) followed by denosumab (24 months)**	
Risk difference (95% CI); p-value	-1.93% (-3.91%, 0.05%); p = 0.056			
Risk ratio (95% CI); p-value	0.23 (0.03, 1.78); p = 0.158			
Odds ratio (95% CI); p-value	0.22 (0.03, 1.77); p = 0.155			
	Month 43		**Month 36**	
Risk difference (95% CI); p-value	**-2.58% (-4.84%, -0.32%); p = 0.025**			
Risk ratio (95% CI); p-value	0.48 (0.16, 1.48); p = 0.203			
Odds ratio (95% CI); p-value	0.47 (0.15, 1.46); p = 0.193			

Source: Table 2-21, 2-32, 2-33, 2-36, pp 88, 122-123, 127 of the submission

ITC = indirect treatment comparison; GCP = Good Clinical Practice

[a] The modified intent-to-treat (mITT) population (excluding the 2 non-GCP sites) comprised patients in the ITT who had the pre-treatment and the post-baseline evaluable radiologic assessment

[b] In ACTIVE, this was the incidences obtained in the mITT population at end of treatment (Month 18); in FRAME, this was the cumulative incidences in the ITT population

Table 6: Summary of the results of the ITC comparing the nonvertebral fractures and clinical fractures in patients receiving abaloparatide for 18 months followed by alendronate for 24 months vs romosozumab for 12 months followed by denosumab for 24 months

Trial	ACTIVE (18 months)[a]		FRAME (12 months)	
Nonvertebral fractures				
Treatment/statistics	**Abaloparatide**	**Placebo**	**Romosozumab**	**Placebo**
n/N (%)	15/696 (2.16)	21/688 (3.05)	56/3,589 (1.56)	75/3,591 (2.09)
Hazard ratio[b] (95% CI); p-value	0.99 (0.72, 1.37); p = 0.972			
Clinical fractures				
n/N (%)	21/696 (3.02)	35/688 (5.09)	58/3,589 (1.62)	90/3,591 (2.51)
Hazard ratio[b] (95% CI); p-value	0.98 (0.74, 1.29); p = 0.882			
	ACTIVExtend		**FRAME extension study**	
Treatment/statistics	**Abaloparatide (18 months) followed by alendronate (24 months)**		**Romosozumab (12 months) followed by denosumab (24 months)**	
Nonvertebral fractures				
	Month 25		Month 24	
Hazard ratio[b] (95% CI); p-value	0.85 (0.61, 1.20); p = 0.356			
	Month 43		Month 36	
Hazard ratio[b] (95% CI); p-value	0.89 (0.69, 1.16); p = 0.404			
Clinical fractures				
	Month 25		Month 24	
Hazard ratio[b] (95% CI); p-value	0.92 (0.69, 1.22); p = 0.561			
	Month 43		Month 36	
Hazard ratio[b] (95% CI); p-value	0.97 (0.77, 1.22); p = 0.791			

Source: Table 2-32, 2-33, 2-36, pp122-123, 127 of the submission
CI = confidence interval; GCP = Good Clinical Practice; ITC = indirect treatment comparison; ITT = intent-to-treat
[a] ITT population excluding the two non-GCP sites
[b] Hazard ratio from a Cox model

6.22 Although the direction of the effects in the indirect comparisons showed improved residual efficacy of abaloparatide in reducing fractures compared to romosozumab, the evaluation noted that the reliability of the results of the indirect comparison may have been impacted by the transitivity issues between the two trials and the results should be interpreted with caution. The transitivity issues comprise the aforementioned differences identified across the ACTIVE and FRAME trials (i.e., the differences in patients' prevalence of vertebral fracture and history of past fractures at baseline, risk for further fractures at baseline, BMD T-score requirements for trial inclusion, treatment period, treatment sequence, definition of the clinical fracture endpoint, and timing and frequency of fracture assessment).

Comparative harms

6.23 There was no indirect comparison of the safety of abaloparatide versus romosozumab presented in the submission. The respective safety analyses of the individual agents (using the ACTIVE trial for abaloparatide and pooled safety data from the romosozumab PI) are discussed below.

Abaloparatide safety

6.24 Table 7 summarises the overall treatment emergent adverse events (TEAEs) in the abaloparatide and placebo arms in the ACTIVE trial.

Table 7: Summary of key adverse events in ACTIVE

	Abaloparatide (N = 694) n (%)	Placebo (N = 687) n (%)
At least 1 TEAE	627 (90.3)	607 (88.4)
At least 1 treatment-related TEAE	296 (42.7)	195 (28.4)
At least 1 Severe TEAE	38 (5.5)	37 (5.4)
At least 1 Severe treatment-related TEAE	7 (1.0)	2 (0.3)
At least 1 Serious TEAE	62 (8.9)	66 (9.6)
Adverse events leading to death	3 (0.4)	3 (0.4)
At least 1 AE leading to discontinuation	68 (9.8)	42 (6.1)

Source: Table 2-29, p115 of the submission; Table 14, pp72 of the ACTIVE Clinical Study Report Addendum
GCP = Good Clinical Practice; TEAE = treatment emergent adverse event
Note: Safety population excluding two non-GCP sites

6.25 In ACTIVE, the assessment of harms in the abaloparatide and placebo arms was double-blinded. There were higher incidence rates of at least 1 treatment related TEAE, severe treatment related TEAEs, and ≥1 AE leading to discontinuation in the abaloparatide arm compared to placebo. Serious TAEs and AEs leading to deaths were similar between the abaloparatide and placebo trial arms. Abaloparatide-treated patients also had a higher incidence of severe treatment related TEAEs and ≥1 AE leading to discontinuation compared to teriparatide treated patients.

6.26 In ACTIVE, patients receiving abaloparatide had higher incidence in treatment related AEs compared to placebo, including tachycardia (1% vs 0), right bundle branch block (0.3% vs 0), orthostatic hypotension (1.0% vs 0.4%), fatigue (1.2% vs 0.3%), muscle spasm (1.6% vs 0.7%), headache (4.5% vs 2.2%) and hypercalciuria (11.7% vs 8.0%), and notably higher incidence in treatment related palpitations (3.6% vs 0.3% in placebo), nausea (5.5% vs 1.3% in placebo), dizziness (7.3% vs 2.6% in placebo), and hypercalcaemia (1.4% vs 0.3% in placebo). The incidence of fall reported in patients receiving abaloparatide in ACTIVE was low (3 patients, 0.4%) and was comparable to the other two treatment arms.

6.27 Adverse events of special interest (AESIs) in ACTIVE were not presented in the submission. These AESIs included: hypercalcemia, hypercalciuria, hypophosphatemia, hypersensitivity, orthostatic hypotension, renal impairment, palpitations, nausea, and dizziness.

6.28 Table 8 summarises the incidence rates of AESIs in the ACTIVE trial.

Table 8: Incidence of AESIs in ACTIVE (Safety population, excluding 2 non-GCP sites)

AESI	Abaloparatide (N = 694) n (%)	Placebo (N = 687) n (%)	Teriparatide (N = 686) n (%)
Hypercalcaemia			
≥ 1 treatment related AE	13 (1.9)	3 (0.4)	29 (4.2)
≥ 1 serious AE	0	0	1 (0.1)
≥ 1 serious treatment related AE	0	0	1 (0.1)
≥ 1 AE leading to discontinuation	2 (0.3)	0	4 (0.6)
Hypercalciuria			
≥ 1 treatment related AE	87 (12.5)	57 (8.3)	96 (14.0)
≥ 1 serious AE	0	0	1 (0.1)
≥ 1 serious treatment related AE	0	0	1 (0.1)
≥ 1 AE leading to discontinuation	1 (0.1)	0	4 (0.6)
Hypersensitivity			
≥ 1 treatment related AE	22 (3.2)	11 (1.6)	32 (4.7)
≥ 1 severe AE	1 (0.1)	0	2 (0.3)
≥ 1 serious AE	2 (0.3)	1 (0.1)	2 (0.3)
≥ 1 serious treatment related AE	0	1 (0.1)	1 (0.1)
≥ 1 AE leading to death	0	0	1 (0.1)
≥ 1 AE leading to discontinuation	6 (0.9)	3 (0.4)	4 (0.6)
Orthostatic hypotension			
≥ 1 treatment related AE	112 (16.1)	34 (4.9)	71 (10.3)
≥ 1 severe AE	6 (0.9)	4 (0.6)	0
≥ 1 serious AE	2 (0.3)	2 (0.3)	4 (0.6)
≥ 1 AE leading to discontinuation	25 (3.6)	6 (0.9)	12 (1.7)
Renal impairment			
≥ 1 AE related to renal impairment	46 (6.6)	47 (6.8)	30 (4.4)
≥ 1 treatment related AE	4 (0.6)	8 (1.2)	2 (0.3)
Palpitations			
≥ 1 AE related to palpitation	59 (8.5)	16 (2.3)	24 (3.5)
≥ 1 treatment related AE	35 (5.0)	4 (0.6)	13 (1.9)
≥ 1 severe AE	1 (0.1)	0	1 (0.;1)
≥ 1 serious AE	1 (0.1)	0	2 (0.3)
≥ 1 AE leading discontinuation	8 (1.2)	2 (0.3)	0
Nausea			
≥ 1 AE related to nausea	62 (8.9)	24 (3.5)	44 (6.4)
≥ 1 treatment related AE	39 (5.6)	10 (1.5)	27 (3.9)
≥ 1 severe AE	1 (0.1)	0	0
≥ 1 serious AE	1 (0.1)	0	0
≥ 1 AE leading to discontinuation	11 (1.6)	2 (0.3)	4 (0.6)
Dizziness			
≥ 1 AE related to dizziness	77 (11.1)	49 (7.1)	57 (8.3)
≥ 1 treatment related AE	51 (7.3)	18 (2.6)	39 (5.7)
≥ 1 severe AE	2 (0.3)	1 (0.1)	0
≥ 1 serious AE	0	1 (0.1)	2 (0.3)
≥ 1 AE leading to discontinuation	10 (1.4)	3 (0.4)	8 (1.2)

Source: Table 19, pp82-83 of the ACTIVE Clinical Study Report Addendum

6.29 In ACTIVE, incidence of all AESIs were higher, or similar, in patients receiving abaloparatide compared to placebo. Incidence of orthostatic hypotension,

palpitations, nausea, and dizziness leading to discontinuation were noticeably higher in the abaloparatide arm compared to placebo.

6.30 The incidence of fall as a TEAE potentially associated with orthostatic hypotension reported in ACTIVE was low (4 [0.5%] in the abaloparatide arm vs 2 [0.2%] in the placebo arm). Risk for falls generally increases in people with decreased muscle strength, decreased mobility, poor nutrition, poor vision or cognition, continence challenges, history of falls (especially injurious falls), chronic medical condition(s) causing fragility, or in people receiving medications that can cause dizziness or hypotension[18] . In ACTIVE, however, the majority of enrolled patients were aged below 75 years (80.1% and 80.6% in the abaloparatide and placebo arms, respectively) and were generally healthy, ambulatory, and without major chronic health conditions. History of prior falls in enrolled patients was unknown. The FRAX® tool used to predict patients' fracture risk in ACTIVE does not take history of falls into account for risk prediction. The incidence of treatment related fall is expected to be higher in real world practice.

6.31 The mechanism of action of abaloparatide involves it working as the agonist of the parathyroid hormone receptor; therefore, it can cause hypercalcaemia that results in increased renal calcification and stone formation. When used in patients with mild or moderate renal impairment, drug-related hypercalcaemia may cause muscle weakness and drowsiness. However, the incidence of TEAEs, serious AEs, treatment related TEAEs, AEs leading to death or AEs leading to study discontinuation were comparable for each treatment arm between the different renal impairment groups in ACTIVE (p84 of the ACTIVE CSR Addendum).

6.32 In general, the safety profile of abaloparatide in ACTIVE aligns with the known safety profile of the drug. The vasodilating effect of abaloparatide on vascular smooth muscle and positive chronotropic/inotropic effects on cardiac muscle can affect the stability of blood pressure or cardiac rhythm which may cause dizziness, fainting, and weakness. Despite being part of the known safety profile, these adverse effects are of particular concern in patients who are mostly advanced in age and are at risk for fall because of decreased muscle strength or mobility, poor vision or cognition, continence challenges, history of falls (especially injurious falls), and major chronic medical condition(s) causing fragility.

6.33 In the ACTIVE trial, the abaloparatide arm had a higher rate of TEAEs leading to discontinuation compared to placebo (9.8% vs 6.0% in placebo). In the abaloparatide arm, the most common TEAEs leading to discontinuation were nausea (1.6% vs 0.3% in placebo), dizziness (1.4% vs 0.4% in placebo), headache (1.2% vs 0.3% in placebo),

[18] Government of Western Australia Department of Health. Risk factors for falls. URL: https://www.health.wa.gov.au/Articles/F_I/Falls-prevention-and-management-in-WA/Research-and-education-in-falls/Risk-factors-for-falls

and palpitations (0.9% vs 0.1% in placebo). Six patients discontinued due to a TEAE of QT prolongation (3 [0.4%] on abaloparatide and 2 [0.2%] on placebo).

6.34 There were eight deaths reported during the ACTIVE study period. None of the deaths were considered by the investigators to be related to study medication. Three deaths occurred in each of the abaloparatide and placebo arms. Causes of death in the abaloparatide arm were sepsis, bronchiectasis, and ischaemic heart disease. Causes of death in the placebo arm were bowel cancer, intestinal obstruction, and sudden death. Causes of death in the teriparatide arm were pancreatic cancer and cardio-respiratory arrest.

Romosozumab safety

6.35 The analysis of romosozumab safety was based on pooled trial data from the Product Information. Common adverse events observed in romosozumab-treated patients included hypersensitivity reactions (rash or dermatitis), headache, cough, arthralgia, neck pain, muscle spasms, and injection site reactions including pain and erythema (Table 2, approved romosozumab PI[19]). Romosozumab has a different mechanism of action compared to abaloparatide and therefore the known safety profile of romosozumab is different, as per the approved romosozumab PI.

6.36 Regarding the cardiovascular safety of romosozumab, the approved romosozumab PI states:[20]

> "In the active-controlled trial of romosozumab for the treatment of severe osteoporosis in postmenopausal women during the 12-month double-blind romosozumab treatment phase, 16 women (0.8%) had myocardial infarction in the romosozumab arm versus 5 women (0.2%) in the alendronate arm and 13 women (0.6%) had stroke in the romosozumab arm versus 7 women (0.3%) in the alendronate arm. These events occurred in patients with and without a history of myocardial infarction or stroke. Cardiovascular death occurred in 17 women (0.8%) in the romosozumab group and 12 women (0.6%) in the alendronate group. The number of women with major adverse cardiac events (MACE = positively adjudicated cardiovascular death, myocardial infarction or stroke) was 41 (2.0%) in the romosozumab group and 22 (1.1%) in the alendronate group, yielding a hazard ratio of 1.87 (95% confidence interval [1.11, 3.14]) for romosozumab compared to alendronate. All-cause death

[19] The safety profile for romosozumab in the approved PI is based on 12-month pooled data from 3,695 postmenopausal women with osteoporosis and 163 men with osteoporosis treated with romosozumab in four Phase II and Phase III, placebo-controlled clinical trials, including the FRAME and BRIDGE studies. The total number of treated patients with either romosozumab or placebo was 7,628.

[20] The summary in the romosozumab PI for myocardial infarction, stroke and mortality is based on a separate double-blind, Phase III active-controlled study (ARCH) of romosozumab vs alendronate, with 2,040 romosozumab-treated patients.

occurred in 30 women (1.5%) in the romosozumab group and 22 women (1.1%) in the alendronate group" (p10 of the approved romosozumab PI).

Clinical claim

6.37 The submission described abaloparatide as non-inferior in terms of efficacy compared to romosozumab.

6.38 Efficacy results in the indirect comparison in terms of preventing new vertebral fractures showed no statistical difference between treatments using relative measures and a statistical advantage for abaloparatide over romosozumab using absolute risk difference. However, the ESC agreed with the evaluation that there were concerns that compromise the transitivity of the abaloparatide (ACTIVE) and romosozumab (FRAME) trials and may impact the validity of the findings from the indirect comparison. Differences between the two trials are described below.

- Study populations' baseline disease severity and risk for further fractures: patients in the ACTIVE trial had a history that included higher incidence of nonvertebral fracture, and placebo treated patients in ACTIVE reported a higher rate of both nonvertebral and clinical fractures, than patients in FRAME. The lowest baseline mean BMD T-score was -2.94 for patients in ACTIVE and -2.76 for patients in FRAME, indicating that patients in ACTIVE had a higher risk for fracture. Due to the different requirements of history of fracture at baseline and the different treatment outcome in the placebo arms in the two trials, ACTIVE may have enrolled a population with a slightly higher risk for further fracture at baseline compared to FRAME. The PSCR stated that the PBAC has previously noted the broadly similar risk of fracture in the two studies (paragraph 6.19, romosozumab PSD, March 2020) while acknowledging some specific between-trial population differences.
- Treatment sequence: the subsequent treatment after cessation of abaloparatide in ACTIVExtend was alendronate, while it was denosumab after cessation of romosozumab in the FRAME extension study. The PSCR stated that the PBAC has previously accepted that alendronate is an appropriate proxy for antiresorptive therapy (paragraph 5.3, romosozumab PSD, March 2024), and that denosumab has improved BMD outcomes over alendronate (p6, denosumab PSD, July 2010).
- Definition of the clinical fracture endpoint: clinical fracture in ACTIVE was defined as all fractures and all levels of trauma causing the fractures, while it was only clinical (symptomatic) vertebral fractures and nonvertebral fractures not associated with severe trauma in FRAME.
- Timing and frequency of fracture assessment: After the baseline assessment, fracture assessment only occurred at the end of treatment in ACTIVE, and twice in ACTIVExtend (Month 6 and Month 24), compared to the monthly

assessments and the assessments outside of the scheduled timepoints when needed in FRAME. The evaluation considered that compared to the FRAME trial, incidences of fracture in ACTIVE and ACTIVExtend are more likely to be unidentified and under-reported.

6.39 Furthermore, the evaluation noted that in both the ACTIVE and FRAME trials, patients who did not have a nonvertebral fracture or clinical fracture event were censored for outcome analyses at the last observation time, hence introducing uncertainties into the outcome analyses.

6.40 The evaluation and the ESC noted that the following factors may affect the applicability of the ACTIVE trial results to the proposed Australian population:

- The ACTIVE trial included patients who were generally healthy and ambulatory, and excluded the more fragile patients including those with ≥4 spine fractures (of any severity) or any severe fracture, and those with comorbidities in other organ systems. In the Australian setting, however, patients with medical conditions that can cause fragility may receive abaloparatide, as per the requested restriction.
- The FRAX® fracture risk score in the study population was lower than the RACGP guideline-suggested FRAX® fracture risk score, indicating a lower fracture risk among the ACTIVE study population compared to the requested treated population who must have a 'very high risk for fracture'.
- The need to inject abaloparatide daily may be burdensome to some patients and reduce compliance in real-world practice. A reduction in compliance relative to what was observed in the ACTIVE trial may impact its relative treatment effect and the claim of non-inferior effectiveness versus romosozumab.

6.41 The PBAC acknowledged the differences between the ACTIVE and FRAME trials that may limit the reliability of the ITC, as well as differences between the ACTIVE trial population and Australian patients that may limit the applicability of the trial results. However, it considered that it is likely that abaloparatide has non-inferior effectiveness compared to romosozumab, and that the ACTIVE trial population and processes of care were sufficiently representative of that seen in Australia. While the PBAC noted that patients assigned to the teriparatide arm in the ACTIVE trial received open-label treatment, the Committee nevertheless considered that the data suggested that abaloparatide was likely to be non-inferior to teriparatide.

6.42 The submission described abaloparatide as superior in terms of safety compared to romosozumab. The evaluation and the ESC considered that this claim was not adequately supported, as it was not based on comparative evidence from the key trials or the indirect comparison, but on data from the ACTIVE trial compared to pooled data from the romosozumab Product Information. Due to the different mechanisms of

action of the two drugs, abaloparatide and romosozumab have different TEAE profiles. The evaluation noted that TEAEs associated with abaloparatide treatment may cause disturbance in cardiac rhythm and blood pressure instability, as well as dizziness, fatigue, and weakness, and considered that occurrence of these AEs may increase the risk for falls in this vulnerable population. However, the PBAC considered that the superiority claim could be reasonably applied to CV-related adverse events, as CV-events are well documented with romosozumab and there is no CV safety concern with abaloparatide. For non-CV-related safety, the PBAC considered that abaloparatide is non-inferior to romosozumab based on data presented in the submission. The PBAC further considered that based on the results of the ACTIVE trial that abaloparatide is likely to be non-inferior to teriparatide with respect to safety.

Economic analysis

6.43 The submission presented a CMA to support the listing of abaloparatide for the first-line treatment of severe osteoporosis. This was based on the claim of non-inferior effectiveness and superior safety compared to romosozumab based on the indirect comparison of the ACTIVE and FRAME trials. Noting issues regarding the transitivity of the ACTIVE and FRAME trials (paragraph 6.38), the presentation of a CMA is reasonable only if the PBAC accept the claim of non-inferior effectiveness.

6.44 The key components of the approach are summarised in Table 9.

Table 9: Key components and assumptions of the cost-minimisation approach

Component	Claim or assumption
Therapeutic claim: effectiveness	Based on the clinical evidence presented, comparative effectiveness is assumed to be non-inferior. Given the differences between key abaloparatide (ACTIVE) and romosozumab (FRAME) trials, this claim may not be adequately supported.
Therapeutic claim: safety	Based on the clinical evidence presented, safety is assumed to be superior. This claim was not based on comparative evidence. Due to the different mechanisms of action of the two drugs, abaloparatide and romosozumab have different TEAE profiles.
Evidence base	Indirect comparison of abaloparatide (ACTIVE) and romosozumab (FRAME)
Equi-effective doses	14.97 scripts (30 × 80 mcg injections per script) of abaloparatide 80 mcg once daily over 18 months of therapy = 10.8 scripts (2 × 105 mg/1.17 mL injections per script) of romosozumab 210 mg once monthly over 12 months of therapy
Direct medicine costs	The cost of abaloparatide is higher per patient per course to account for a reduction in attendances for administrations, anti-resorptive therapies and cardiovascular monitoring and events.
Other costs or cost offsets	A reduction in the use and cost of health professional attendances for administration, anti-resorptive therapies (to balance treatment period), cardiovascular monitoring and cardiovascular event management.

Source: Constructed during the evaluation.
TEAE = treatment-related adverse event.

6.45 The submission proposed the equi-effective doses as:

30 abaloparatide injections (80 mcg per injection) monthly =

2 romosozumab injections (105 mg/1.17 mL per injection) monthly.

However, including duration of therapy, the equi-effective doses were estimated by the evaluation as:

Abaloparatide 80 mcg injection per day for 14.97 months =

Romosozumab 2 × 105 mg/1.17 mL injections per month for 10.8 months.

6.46 The duration of therapy of abaloparatide in the submission was based on the mean exposure to abaloparatide treatment observed in the ACTIVE trial (14.97 months). While this accounts for the total time on treatment, the evaluation noted that it does not account for dose interruptions or reduced compliance to treatment. Compliance in the trial was high (97.8%), though is likely to be further reduced in practice. Based on the mean number of doses administered of 439.4, the number of scripts over 18 months was equal to 14.65. For romosozumab, the submission estimated the average number of scripts from the mean number of doses administered in the FRAME trial (10.8 doses over 12 months) (paragraph 6.42, romosozumab PSD, July 2019). The impact of differences between observed and expected compliance on the claim of similar comparative efficacy with romosozumab was not considered in the submission. Given the differences in the frequency of administration, the evaluation considered that it is plausible that compliance to abaloparatide in practice may be lower than compliance to romosozumab. The PBAC considered that the durations of therapies of both the agents should be based on the maximum duration of therapy in the respective Product Information (18 months for abaloparatide and 12 months for romosozumab), as the persistence and adherence to each agent is uncertain.

6.47 The submission noted that romosozumab has a special pricing arrangement with the sponsor being unaware of the effective price, and that while romosozumab has the same published price across its first- and second-line listings, effective pricing is weighted on use (75% and 25%, respectively in the first- and second-line settings), with a slightly higher indication-specific price in the second line setting (paragraph 5.12, romosozumab PSD, March 2024). On this basis, the submission estimated a published approved ex-manufacturer price (AEMP) for romosozumab in the first-line setting, based on the expected distribution of use, assuming an AEMP in the first-line setting 10% lower than that in the second line setting. The estimated AEMP for romosozumab in the first-line setting, which was assumed by the submission on the basis of the above and which was applied in the analysis, was $[redacted]. In comparison, the published romosozumab AEMP for both first- and second-line therapy is $352.24.

6.48 The submission included the cost of health professional attendances for administration, and changes in the use and cost of anti-resorptive therapies, cardiovascular monitoring and cardiovascular event management. While the types of resources included were consistent with costs associated with romosozumab when previously considered by the PBAC (Table 8, romosozumab PSD, March 2020), conservative assumptions for these additional costs had been applied (paragraph 6.48, romosozumab PSD, March 2020). The evaluation considered that there is a risk

that the extent of some of the cost offsets included in the present CMA may not be realised, which may lead to an overestimation in the cost-minimised price for abaloparatide. The PSCR and pre-PBAC response disagreed that conservative costs previously included in the cost-minimisation of romosozumab in the second-line setting versus teriparatide may not be realised for abaloparatide.

6.49 The submission assumed that only the first dose of abaloparatide would require a health care professional attendance. The evaluation considered that this was reasonable. In contrast, every dose of romosozumab was assumed to require a health care professional attendance. While this was consistent with administration in the romosozumab trials and with previous PBAC consideration (paragraph 6.51, romosozumab PSD, July 2019), the evaluation noted that romosozumab may be self-administered. This was not considered in the submission and may overestimate administration costs associated with romosozumab. The cost of administration per course of romosozumab was based on an average of the cost where administrations were provided by GPs only ($406.08, as reported in paragraph 6.56, romosozumab PSD, March 2020) and a weighted cost that included administration by both GPs (MBS item 23, $42.85 per administration in 31% of patients) and nurses (MBS item 82200, $14.20 per administration in 69% of patients). While the ESC considered that it was unrealistic to assume abaloparatide would be administered completely by patients (apart from the first dose) and romosozumab would never be administered by patients, the PBAC considered that it would be reasonable to include the treatment administration costs for both abaloparatide and romosozumab in the CMA as presented in the submission.

6.50 Following completion of romosozumab treatment, the cost of subsequent ART was applied for the difference (175 days) in the maximum durations of abaloparatide (540 days) and romosozumab (365 days) treatment. The PBAC agreed with the evaluation that it would not be reasonable to include this cost given that use of romosozumab for a shorter duration of time (12 months) than abaloparatide (18 months) would not lead to an increased duration of ART, it would just be earlier initiation of treatment. Further, the submission has assumed 100% compliance to subsequent ART, which is likely to be an overestimate. When romosozumab was considered in the first-line setting, adherence to subsequent ART assumed was 90% (Table 6, romosozumab PSD, March 2024). The average cost per day ($0.95) was based on the AEMP for denosumab 60 mg, alendronate 70 mg and risedronate (daily, weekly and monthly presentations), accounting for assumed days of coverage per script and distribution of use (59.8% denosumab, 6.5% alendronate, 34.0% risedronate). The PBS items used to derive the cost per day excluded alendronate with vitamin D formulations, though included the risedronate item for symptomatic Paget disease of bone. Further, the duration of 60-day alendronate scripts was not correctly accounted for. These changes reduced the cost per day to $0.90, driven by a higher proportion of alendronate scripts (13.6% vs

6.5%). The PSCR stated (p5) that the Sponsor accepted the evaluation's changes to the subsequent ART costs in the CMA (from $0.95 to $0.90).

6.51 The cost of additional ART was also applied in patients who prematurely discontinued either abaloparatide or romosozumab treatment (6 months in 20% of patients). No difference was assumed across the treatment arms. The evaluation considered that the basis for the inclusion of this cost was not clear. Previously, additional costs were conservatively included to account for residual treatment effects associated with teriparatide but not romosozumab (paragraph 6.56, romosozumab PSD, March 2020). The PSCR stated (p5) that the Sponsor accepted removing the costs of additional ART for patients who discontinued either abaloparatide or romosozumab treatment, noting that they cancel out in the CMA.

6.52 Given the potential cardiovascular risks associated with romosozumab use, the submission included the cost of cardiovascular monitoring while on romosozumab treatment and the cost of cardiovascular event management. The PBAC agreed with the evaluation that this was reasonable. Resource use and sources for unit costs of monitoring were consistent with previous submissions to the PBAC for romosozumab (paragraph 6.48, romosozumab PSD, July 2019).

6.53 The cost per cardiovascular event applied was $182.17, and was attributed to hospitals and patients, assuming an incidence of 0.59% (based on the ARCH trial). The evaluation considered that this was reasonable given that costs previously presented to the PBAC included hospitalisation and out-of-hospital costs (paragraph 6.58, romosozumab PSD, March 2020). The cost per event to hospitals ($15,484) was derived from the average price weight for AR-DRG F10[21] (2.40) and applied to the National Efficient Price ($6,465). The evaluation considered that other AR-DRGs (F41 and F60) should have been included. As these omitted DRGs are associated with a lower cost, the evaluation noted that the cost applied per event has likely been overestimated. The average cost to hospitals per patient treated with romosozumab was estimated to be $91.09.[22] An equal cost ($91.09 i.e. $15,484 per patient with a cardiovascular event) was assumed to be borne as out-of-pocket costs by patients. The evaluation considered that this assumption relating to out-of-pocket costs was not likely to be supported. A prospective Australian study[23] reporting the direct health care costs associated with initial hospitalisation and the 12-month sequelae for patients with a first-ever MI observed that out-of-pocket expenses accounted for 8% of the total direct cost of a first-ever MI episode (compared to 50% assumed in the

[21] Interventional Coronary Procedures, Admitted for acute myocardial infarction

[22] Incidence of cardiovascular event (0.59%) × hospitalisation cost per event ($15,484)

[23] Ioannides-Demos LL, Makarounas-Kirchmann K, Ashton E, Stoelwinder J, McNeil JJ. Cost of myocardial infarction to the Australian community: a prospective, multicentre survey. *Clin Drug Investig*. 2010;30(8):533-43.

submission base case).

6.54 The results of the CMA, based on an estimated published AEMP for romosozumab in the first line setting, is presented in Table 10.

Table 10: Results of the cost-minimisation approach, based on published prices

Component	Abaloparatide	Romosozumab
AEMP per script	$[redacted]	$[redacted] [b]
No. scripts per course	14.97 [a]	10.80 [c]
Total medicines cost per course	**$[redacted]**	**$[redacted]**
Cost of healthcare professional attendances for administration	$42.85	$328.04
Cost of 6 months additional anti-resorptive therapy in patients who discontinue study drug prematurely	$34.83	$34.83
Cost of subsequent anti-resorptive therapy to balance of total treatment period (175 days)	–	$167.02
Cost of cardiovascular monitoring	–	$190.10
Cardiovascular event management	–	$182.17
Total cost per course	**$[redacted]**	**$[redacted]**

Source: Adapted from Table 3–3, p150 of the submission.
Note: The use of published pricing may not represent the average cost per patient per course of treatment after the impact of special-pricing and risk-sharing arrangements are accounted for.
[a] over a maximum treatment course of 540 days therapy
[b] published price as estimated by the sponsor
[c] over a maximum treatment course of 365 days therapy

6.55 The ESC noted that the cost-minimised price for abaloparatide was sensitive to the assumed treatment durations, with a sensitivity analysis showing that if abaloparatide and romosozumab are both used for their maximum treatment durations of 18 months and 12 months, respectively, that the cost-minimised price for abaloparatide would be reduced by approximately [redacted]% from $[redacted] to $[redacted] (Table 11).

Table 11: Sensitivity analysis assuming the maximum durations of abaloparatide or romosozumab treatment, based on published prices

Component	Abaloparatide	Romosozumab
AEMP per script	$[redacted]	$[redacted] [b]
No. scripts per course	18.0 [a]	12.0 [c]
Total medicines cost per course	**$[redacted]**	**$[redacted]**
Cost of healthcare professional attendances for administration	$42.85	$341.89
Cost of 6 months additional anti-resorptive therapy in patients who discontinue study drug prematurely	$34.83	$34.83
Cost of subsequent anti-resorptive therapy to balance of total treatment period (175 days)		$167.02
Cost of cardiovascular monitoring		$190.10
Cardiovascular event management		$182.17
Total cost per course	**$[redacted]**	**$[redacted]**

Source: Adapted from Table 3–3, p150 of the submission.
Note: The use of published pricing may not represent the average cost per patient per course of treatment after the impact of special-pricing and risk-sharing arrangements are accounted for.
[a] over a maximum treatment course of 540 days therapy
[b] published price as estimated by the sponsor
[c] over a maximum treatment course of 365 days therapy

6.56 The cost per patient for treatment with abaloparatide in the submission was $[redacted] (drug cost, administration cost and additional anti-resorptive therapy cost), which was the same as the cost per patient for treatment with romosozumab (based on the estimated published drug cost, administration cost, cardiovascular event management and monitoring cost, subsequent anti-resorptive therapy cost, additional anti-resorptive therapy cost). The evaluation noted that should the PBAC accept the clinical claim of overall non-inferior effectiveness, the CMA must establish that the cost per patient for treatment with abaloparatide would be no more than the cost per patient of romosozumab. Where these cost-per-patient calculations are uncertain, the guiding principle is that the Australian Government should not bear the financial risk of this uncertainty because the Australian population already has access to therapy that is proposed to be at least as effective.

6.57 The PBAC noted that teriparatide and romosozumab are both PBS-listed in the second-line setting (see paragraphs 5.3 and 5.4) and considered that it would be reasonable for a CMA for abaloparatide in the second-line setting to be based on the least costly alternative of romosozumab or teriparatide, noting the maximum treatment duration is 12 months for romosozumab and 18 months for teriparatide.

Drug cost/patient/course

6.58 The cost per patient per course of abaloparatide was $[redacted], estimated from the cost-minimised dispensed price for maximum quantity (DPMQ) ($[redacted] per script) based on an estimated published price for romosozumab in the first line setting, assuming 14.97 scripts per course of treatment. The cost per patient per course of romosozumab was $4,386.20, based on the published DPMQ ($406.13) at the time of the evaluation, assuming 10.8 scripts per course of treatment. Based on the published DPMQ of $177.30 for teriparatide, the ESC noted that the cost per patient per course would be $[redacted], assuming one script per month for the maximum treatment duration of 18 months.

6.59 A comparison of the use and costs applied across the trials, economic and financial analyses is presented in Table 12. While use of abaloparatide and romosozumab was consistent across the economic and financial analyses, differences in the costs applied per course were noted, due to the use of AEMP and DPMQ prices, respectively. The cost of ARTs subsequent to romosozumab was also noted to differ across the economic and financial analyses, as the submission had not correctly accounted for the duration of coverage of anti-resorptive scripts. This was revised during the evaluation.

Table 12: Drug cost per patient for abaloparatide, romosozumab and subsequent use of anti-resorptive therapy

	Abaloparatide			Romosozumab		
	Trial dose and duration	Economic analysis	Financial estimates	Trial dose and duration	Economic analysis	Financial estimates
First line treatment						
Treatment adherence	97.8%	100%	100%	Not reported [a]	90% [b]	90% [b]
Treatment persistence	Overall exposure duration was 14.97 months	14.97 months	14.97 months	Mean doses administered was 10.8		
Mean no. scripts per patient	14.97	14.97	14.97	10.8	10.8	10.8
Cost per script [f]	–	$	$	–	$	$406.13
Cost per course [f]	–	$	$	–	$	$4,386.20
Anti-resorptive therapy						
Additional anti-resorptive therapy in patients who discontinue treatment	Not reported	6 months in 20% of patients	–	Not reported	6 months in 20% of patients	–
Subsequent anti-resorptive therapies per patient treated [c]	Not reported	–	–	Not reported	175 days [d]	2.7 scripts [e]
Anti-resorptive drug cost	–	$34.83	–	–	$201.85	$436.90 (revised: $220.56)

Source: Constructed during the evaluation.
[a] Drug exposure data (i.e. reported as mean doses administered) did not differentiate between adherence and persistence.
[b] Adherence and persistence were not separately considered.
[c] To make up difference in duration of first line treatment
[d] Use and cost estimated on a per day basis, weighted 60% denosumab, 6% alendronate; and 34% risedronate, assuming 100% compliance
[e] Weighted 61% denosumab; 6% alendronate; and 33% risedronate, assuming 90% compliance.
[f] Cost per script and cost per course for romosozumab are based on estimated first-line published price for the economic analysis and the DPMQ For the financial estimates

Estimated PBS usage & financial implications

6.60 This submission was not considered by DUSC.

6.61 The submission used an abridged epidemiological approach (based on the estimated number of patients expected to receive romosozumab treatment in the first line setting) combined with an uptake rate to estimate the use and financial impact of listing abaloparatide for the first line treatment of severe osteoporosis. A conventional market share approach could not be employed due to the lack of utilisation data for first-line romosozumab use (recently reimbursed on the PBS since November 2024). A summary of the data sources and parameter values used is presented in Table 13.

Table 13: Key inputs for financial estimates

Parameter	Value applied and source	Evaluation comment
Incident patients expected to receive first line treatment with romosozumab	[redacted][1] in Year 1, increasing to [redacted][2] in Year 6 estimated from ranges reported in Table 7, romosozumab PSD, March 2024.	The resulting estimates are likely to be associated with considerable uncertainty. Differences between the populations eligible for abaloparatide and romosozumab were not considered (e.g. abaloparatide is TGA-approved for use in post-menopausal women, and is also likely to be used in those patients contraindicated to romosozumab or those who develop intolerance to ARTs or romosozumab of a severity necessitating permanent treatment withdrawal within the first 6 months of therapy, as per the requested restriction.
Uptake rate of abaloparatide	Assumed to increase from [redacted]% in Year 1, to [redacted]% in Year 6	Based on the claim of reduced cardiac events, this may be reasonable.
Abaloparatide compliance	83.16%, based on the average months on treatment (14.97) in the ACTIVE trial, divided by maximum duration of treatment (18 months)	This estimate may reflect persistence to treatment rather than adherence while on treatment, which should apply in addition to persistence.
Reduction in romosozumab scripts	10.8 romosozumab scripts per replaced patient, based on the application of a 90% adherence rate to the maximum 12 scripts	The PBAC previously noted that a 20% discontinuation rate would likely be the minimum anticipated in practice (paragraph 7.10, romosozumab PSD, July 2022) and was applied in addition to trial-based adherence (Table 6, romosozumab PSD, March 2024).
Reduction in use of subsequent anti-resorptive scripts per patient	2.7 scripts per replaced patient, based on six scripts per year on treatment, assuming 90% compliance, where each patient was assumed to receive 6 months (i.e. 0.5 year) treatment	A reduction in the use of ART may only be reasonable if abaloparatide reduces the duration of ART (not just later initiation of treatment). This approach also did not consider the duration of coverage of scripts for each ART. This therefore overestimated the reduction in denosumab scripts, which was associated with the highest cost. The impact to the PBS/RPBS was revised during the evaluation to account for differences in script frequency between the different ARTs.
Abaloparatide	$[redacted], based on the proposed published DPMQ	Reasonable.
Romosozumab	$406.13, based on PBS item 14641N	Reasonable.
Denosumab	$251.97, based on PBS item 5457F	Reasonable.
Alendronate	$17.69, based on the weighted DPMQ of PBS items 8511Y and 13499L	These items are for alendronate use alone (i.e. without vitamin D) and provide 30 days and 60 days' supply, respectively. As the reduction in scripts did not account for different durations of supply, it is not appropriate to apply a weighted cost.
Risedronate	$21.37, based on the weighted DPMQ of PBS items 13499L and 2191H	The PBS items used to determine the weighted price erroneously included an alendronate item which represented 99.4% of the estimated weighted price.
Affected MBS items		
GP attendance	$34.28 [a] based on MBS item 23	It was not appropriate to assume a reduction in use and cost of GP services, as these will not likely be realised.
Nurse attendance	$11.36 [a] based on MBS item 82200	Reasonable.

Parameter	Value applied and source	Evaluation comment
Specialist attendance	$39.80 [a] based on MBS item 115	
ECG	$28.48 [a] based on MBS item 11704	
Blood tests	$7.76 [a] based on MBS item 66500	

Source: Constructed during the evaluation from the submission and the 'Abaloparatide - Eladynos - Section 4 - Base Case - 8 March 2025.xlsx' file.
ART = anti-resorptive therapy; ECG = electrocardiogram; GP = general practitioner; PSD = public summary document.
[a] Assuming the 80% level of rebate
The redacted values correspond to the following ranges:
[1]5,000 to < 10,000
[2]20,000 to < 30,000

6.62 The submission estimated the size of the severe osteoporosis market eligible for treatment from when romosozumab was considered for listing in the first line setting (Table 12, romosozumab PSD, March 2024). The submission applied the percentages for first line romosozumab use to the patient-number ranges shown in the PSD to estimate the market size. The submission considered that the availability of abaloparatide would not be expected to result in additional patients being diagnosed or treated for severe osteoporosis. This does not consider that there may be patients eligible for abaloparatide who are not eligible for romosozumab – such as patients with a history of myocardial infarction or stroke who are contraindicated for romosozumab, or those who develop an intolerance to ARTs or romosozumab.

6.63 The submission assumed that the listing of abaloparatide would reduce the use of romosozumab in the first line setting (10.8 scripts per replaced patient per course). The evaluation considered that this was reasonable. The submission also assumed a reduction of 2.7 scripts[24] per replaced patient of subsequent ART, distributed by use (denosumab: 61%, alendronate: 6%; and risedronate: 33%). The evaluation considered that a reduction in the use of ART may only be reasonable if abaloparatide reduces the duration of ART (not just later initiation of treatment). Further, the submission did not consider differences in script frequency between the different ARTs (e.g. denosumab is 6-monthly, compared to alendronate and risedronate which are prescribed every 1–2 months).

6.64 The submission's estimates for the number of patients treated and financial impact of abaloparatide over the first 6 years of listing is presented in Table 14.

[24] Based on a reduction of 6 months of anti-resorptive therapy (50% year), where patients would reduce 6 scripts per year, at 90% compliance (50% × 6 × 90%)

Table 14: Estimated use and financial implications (based on published pricing)

	2025	2026	2027	2028	2029	2030
Estimated extent of use						
Total no. patients initiating treatment in the 1L setting	[redacted][1]	[redacted][2]	[redacted][2]	[redacted][2]	[redacted][2]	[redacted][3]
Market share of abaloparatide	[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%
No. patients electing abaloparatide treatment	[redacted][4]	[redacted][4]	[redacted][4]	[redacted][1]	[redacted][1]	[redacted][2]
No. scripts (9.98 per year on treatment)	[redacted][2]	[redacted][5]	[redacted][6]	[redacted][7]	[redacted][8]	[redacted][8]
Estimated financial implications of abaloparatide						
Cost to PBS/RPBS less copayments	$[redacted][9]	$[redacted][10]	$[redacted][11]	$[redacted][12]	$[redacted][13]	$[redacted][14]
Estimated financial implications for changes in use of other affected medicines						
Reduction in cost of romosozumab to the PBS/RPBS less copayments	$[redacted][9]	$[redacted][10]	$[redacted][11]	$[redacted][11]	$[redacted][13]	$[redacted][15]
Reduction in cost of anti-resorptive therapies to the PBS less copayments Revised [a]	$[redacted][9] $[redacted][9]	$[redacted][9] $[redacted][9]	$[redacted][9] $[redacted][9]	$[redacted][9] $[redacted][9]	$[redacted][9] $[redacted][9]	$[redacted][9] $[redacted][9]
Net cost to the PBS/RPBS **Revised [a]**	**−$[redacted][16]** **−$[redacted]**	**−$[redacted][16]** **$[redacted][9]**	**−$[redacted][16]** **$[redacted][9]**	**−$[redacted][16]** **$[redacted][9]**	**$[redacted][9]** **$[redacted][9]**	**$[redacted][9]** **$[redacted][9]**
Net impact to the MBS Revised [b]	−$[redacted][16] −$[redacted][16]	−$[redacted][16] −$[redacted][16]	−$[redacted][16] −$[redacted][16]	−$[redacted][16] −$[redacted][16]	−$[redacted][16] −$[redacted][16]	−$[redacted][16] −$[redacted][16]
Impact to state hospital budgets [c]	−$[redacted][16]	−$[redacted][16]	−$[redacted][16]	−$[redacted][16]	−$[redacted][16]	−$[redacted][16]
Net impact to Government health budgets **Revised [a, b, c]**	**−$[redacted][16]** **−$[redacted][16]**	**−$[redacted][16]** **−$[redacted][16]**	**−$[redacted][16]** **−$[redacted][16]**	**−$[redacted][16]** **−$[redacted][16]**	**−$[redacted][16]** **−$[redacted][16]**	**−$[redacted][16]** **−$[redacted][16]**

Source: Constructed during the evaluation from the submission and the 'Abaloparatide - Eladynos - Section 4 - Base Case - 8 March 2025.xlsx' file.

1L = first line.

Note: The use of published pricing may not represent the financial impact to the respective Government health budgets following the application of special-pricing and risk-sharing arrangements.

[a] Impact to the PBS/RPBS was revised to account for differences in script frequency between the different anti-resorptive therapies, assuming only 30-day supply scripts (which represents >90% of current supply) for alendronate or risedronate.

[b] Impact to the MBS was revised during the evaluation to exclude the impact on GP services and to reduce the number of nurse attendances applied per patient for consistency with the cost-minimisation approach (50% of 10.8 × 69%)

[c] Reduction in costs for cardiovascular event management

The redacted values correspond to the following ranges:

[1] 5,000 to < 10,000

[2] 10,000 to < 20,000

[3] 20,000 to < 30,000

[4] 500 to < 5,000

[5] 30,000 to < 40,000

[6] 60,000 to < 70,000

[7] 90,000 to < 100,000

[8] 100,000 to < 200,000

[9] $0 to < $10 million

[10] $10 million to < $20 million

[11] *$20 million to < $30 million*
[12] *$30 million to < $40 million*
[13] *$40 million to < $50 million*
[14] *$60 million to < $70 million*
[15] *$50 million to < $60 million*
[16] *net cost saving*

6.65 The total cost to the PBS/RPBS of listing abaloparatide (based on published pricing) was estimated to be $0 to < $10 million in Year 6, with a cost-saving of $0 to < $10 million over the first 6 years of listing. Estimates were revised during the evaluation to correctly account for differences in script frequency between the different anti-resorptive therapies. The revised total cost to the PBS/RPBS was estimated to be $0 to < $10 million in Year 6, and a total of $0 to < $10 million in the first 6 years of listing.

6.66 Cost savings to the PBS/RPBS are observed in the first year of listing as this compares a full course of romosozumab treatment relative to two-thirds of a course of abaloparatide in those patients who initiate in the first year of listing. In subsequent years, net costs to the PBS/RPBS are observed, which is consistent with the cost-minimised price which included offsets for reduced treatment administration and cardiovascular monitoring medical services, in addition to a reduction in hospitalisation costs for management of cardiovascular events.

6.67 The submission assumed that the listing of abaloparatide would lead to a net reduction in GP and nurse attendances for treatment administration and a reduction in services for cardiovascular monitoring. The evaluation noted that while this was consistent with affected medical services included in the CMA, the estimated cost savings are not likely to be realised due to the demand on GP services. The submission assumed a reduction of 8.28 nurse attendances for romosozumab administration derived from the maximum number of doses per patient (12), assuming 69% would be performed by nurses. It was not reasonable to assume a higher reduction of services for treatment administration (12) than for doses of romosozumab (10.8). Further, the proportion of services delivered by nurses was not consistent with what was applied in the base case economic analysis (34.5%)[25] (equivalent to 3.73 per patient treated). The PSCR maintained that GP costs should have been included in the financial estimates.

6.68 The submission assumed that the reduction in romosozumab use would also be associated with a reduction in the number of cardiovascular events managed in hospitals, due to the reduced incidence of treatment-related MI and stroke, assuming an average cost of $91.09 per patient treated (paragraph 6.53) with an 80% rebate applied. Application of an 80% rebate to the hospitalisation costs was not appropriate.

[25] 50% of administration cost was GP only, with the remaining 50% split between nurses (69%) and GPs (31%). Overall, the proportion of services provided by nurses was 50% × 69% = 34.5%

Quality Use of Medicines

6.69 The submission outlined the following:

- Abaloparatide is a drug that has less cardiac safety concern and causes less incidence of hypercalcaemia.
- Abaloparatide is available in a pen injector device for daily self-injection and does not require refrigeration.
- The sponsor will provide clinician support and education programs for health professionals
- The sponsor will provide patient support program and patient kits.

As abaloparatide has a short half-life (approximately 1 hour), this allows for flexibility in managing adverse effects and adjusting therapy. However, the evaluation considered that the daily injection requirement may become a burden in some patients and may affect the treatment compliance. Also, the safety of abaloparatide in terms of increasing the risk of falls might be a concern in the quality use of this drug.

Financial Management – Risk Sharing Arrangements

6.70 The submission did not propose a risk-sharing arrangement (RSA). However, there is a RSA that covers use of romosozumab in the first- and second-line settings. Given the proposed substitution of romosozumab by abaloparatide, the evaluation noted that it may be appropriate for abaloparatide to join this RSA.

For more detail on PBAC's view, see section 7 PBAC outcome.

7 PBAC Outcome

7.1 The PBAC recommended the General Schedule Authority Required listing of abaloparatide for the treatment of patients with severe established osteoporosis and very high risk of fracture. The PBAC considered that it would be appropriate for the PBS listings for abaloparatide to allow use in either the first or second-line settings, consistent with the listings for the main comparator, romosozumab. The PBAC's recommendation for listing was based on, amongst other matters, its assessment that the cost-effectiveness of abaloparatide would be acceptable if it were cost minimised to romosozumab in the first-line (1L) setting, and to the least costly alternative of teriparatide or romosozumab for second-line (2L) use. The PBAC considered the evidence presented in the submission demonstrated that abaloparatide has non-inferior effectiveness, a superior safety profile with respect to cardiovascular (CV) events, and a non-inferior safety profile with respect to other adverse events compared to romosozumab.

7.2 The PBAC considered that a cost-minimisation approach (CMA) to romosozumab in the 1L setting, and to the least costly alternative of romosozumab or teriparatide in

the 2L setting would be appropriate.

7.3 The PBAC considered the equi-effective doses for 1L use were:

- Abaloparatide 80 microgram per day for 18 months;
- Romosozumab 210 mg once per month for 12 months.

The PBAC considered the equi-effective doses for 2L use were:

- Abaloparatide 80 microgram per day for 18 months;
- Romosozumab 210 mg once per month for 12 months;
- Teriparatide 20 microgram per day for 18 months.

7.4 The PBAC noted that there was a moderate clinical need to have an alternative anabolic treatment for osteoporosis on the PBS, in particular for patients unable to tolerate or who have a contraindication to romosozumab. The PBAC noted the consumer comments to this effect and acknowledged the increasing evidence to suggest that anabolic agents should be used 1L to build new bone, yet some patients do not have access to 1L anabolic treatment due to cardiovascular contraindications.

7.5 The PBAC considered that the restrictions for abaloparatide should generally be consistent with the restrictions for romosozumab. The Committee noted that the restrictions should be gender agnostic and specify a lifetime maximum of 18 months (compared with 12 months for romosozumab).

7.6 The PBAC noted that as anabolic treatments are limited to once per lifetime, flow-on changes to the restrictions for romosozumab and teriparatide would be required to prevent sequential therapy for patients who had previously received treatment with abaloparatide.

7.7 The PBAC accepted the proposed comparator of romosozumab in the 1L setting, given that it is the RACGP-recommended 1L therapy for osteoporotic men and post-menopausal women with very high risk of fracture. Notwithstanding, the PBAC noted that romosozumab may not be an appropriate comparator for patients who have CV-related contraindications to romosozumab and that the size of this population is uncertain. Further, the PBAC noted that teriparatide is listed as a 2L treatment and was a comparator to abaloparatide in the pivotal ACTIVE trial for the secondary outcomes of BMD and for safety. The PBAC considered that in the 2L setting, both teriparatide and romosozumab should be considered appropriate comparators.

7.8 The PBAC noted that the pivotal trial evidence presented in the submission, which informed the indirect comparison and CMA, was based on one randomised controlled trial (RCT) of abaloparatide (ACTIVE) and one RCT of romosozumab (FRAME). The PBAC acknowledged the differences between the ACTIVE and FRAME trials that may limit the reliability of the ITC due to transitivity issues, as well as differences between the ACTIVE trial population and Australian patients that may limit the applicability of the trial results. However, overall, the Committee considered that the claim of non-

inferior comparative effectiveness of abaloparatide to romosozumab was adequately supported by the data, and that the ACTIVE trial population and processes of care were sufficiently representative of that seen in Australia.

7.9 The Committee further noted the results of the ACTIVE trial included a comparison of abaloparatide to teriparatide (Figures 1 and 2) and that the comparisons were limited because patients in the teriparatide arm were treated open label. However, notwithstanding this limitation, the Committee considered it would be reasonable to consider that the data was suggestive of non-inferiority. The Committee further considered that it would be reasonable to consider that the results of the ACTIVE trial and the ITCs presented could be extended to the 2L setting.

7.10 With respect to clinical safety, the PBAC considered that the claim of superior comparative safety of abaloparatide could be reasonably applied noting the CV-related adverse events with romosozumab, and that access to abaloparatide would assist patients who are unable to tolerate romosozumab. The PBAC additionally considered that based on data from the ACTIVE trial, and data from the romosozumab Product Information, that abaloparatide is non-inferior to teriparatide, and non-inferior to romosozumab for non-CV-related safety.

7.11 For 1L use, the PBAC supported the submission's approach to present a CMA on the basis that abaloparatide and romosozumab are non-inferior in terms of effectiveness and non-CV safety, and that abaloparatide is superior to romosozumab for CV safety. The PBAC noted that the CMA in the submission accounted for:

- the cost of the medicines;
- the abaloparatide and romosozumab treatment durations based on exposure in the ACTIVE and FRAME trials, respectively (paragraph 6.46);
- the cost of professional attendances for administration (higher cost for romosozumab than abaloparatide, paragraph 6.49);
- the cost of additional ART in patients who discontinue anabolic treatment prematurely (equal cost for both drugs that cancels out in the CMA, paragraph 6.51);
- the cost of subsequent ART to balance the total treatment period for romosozumab (paragraph 6.50);
- the cost of CV monitoring and event management for romosozumab (paragraph 6.52).

The PBAC accepted the submission's approach of including a higher administration cost for romosozumab than abaloparatide and including costs for CV monitoring and event management for romosozumab. However, the PBAC considered that the persistence and adherence to both agents in the community would be uncertain and therefore advised that duration of treatment in the CMA should be based on the maximum duration in the respective Product Information (18 months for abaloparatide and 12 months for romosozumab). The PBAC also considered that the

cost of subsequent ART to balance the total treatment period for romosozumab should be excluded, as ART would be brought forward rather than having an extended treatment duration. As such, the PBAC accepted the sensitivity analysis for the CMA as detailed in Table 11, with the exception that the cost of $167.02 for the cost of subsequent ART 'to balance of total treatment period (175 days)' should be excluded, and noting that the CMA should use the actual AEMP for romosozumab rather than the AEMP estimated by the submission.

7.12 The PBAC considered that restricting abaloparatide to 1L use on the PBS would not be reasonable. As per paragraph 7.7, the PBAC considered teriparatide and romosozumab to be appropriate comparators for 2L treatment of severe established osteoporosis and in this setting the Committee recommended that it would be appropriate for abaloparatide to be PBS-listed at the same cost per course as the least costly alternative of either romosozumab or teriparatide. The PBAC considered that in determining the least costly alternative, that for (1) romosozumab, this should be determined using the effective AEMP for romosozumab in the 2L setting and the same parameters as the Committee recommended for the CMA in the 1L setting (paragraph 7.11); and that for (2) teriparatide, the treatment duration for both abaloparatide and teriparatide should be 18 months. The PBAC noted that the lifetime maximum treatment duration for teriparatide on the PBS is 18 months and that the maximum treatment duration for abaloparatide, based on the Product Information is also 18 months.

7.13 The PBAC noted that as romosozumab for the 1L treatment of severe osteoporosis had only been listed on the PBS since November 2024, a market share approach could not be used to estimate the utilisation of abaloparatide. The PBAC considered that there were several uncertainties associated with the inputs employed in the epidemiological approach, including (1) not considering that there may be patients eligible for abaloparatide who are not eligible for romosozumab (patients with a history of myocardial infarction or stroke who are contraindicated for romosozumab, or those who develop an intolerance to romosozumab); and (2) assuming a reduction in the use of ART when it may only involve the later initiation of treatment, not a change in treatment duration (consistent with the CMA). Further, the submission did not consider differences in script frequency between the different ARTs, although this was corrected during the evaluation.

7.14 The PBAC considered that the financial cost to Government for abaloparatide in the 1L setting would be acceptable if the PBAC-recommended parameters were applied to the CMA (see paragraph 7.11). The PBAC noted that the submission did not estimate utilisation for 2L use, however the listing for abaloparatide would not increase cost to Government in either line of use if it was listed on the basis of a CMA to the least costly alternative in 1L and 2L.

7.15 To account for the uncertainties associated with the financial estimates as detailed in paragraph 7.1313, and as abaloparatide is expected to replace use of romosozumab

in some patients, the PBAC advised that abaloparatide would be required to join the RSA that covers the use of first- and second-line romosozumab with no increase in the expenditure caps.

7.16 The PBAC recommended that abaloparatide should not be treated as interchangeable with any other drugs under Section 101 (3BA) of the *National Health Act 1953*.

7.17 The PBAC advised that abaloparatide is not suitable for prescribing by nurse practitioners. The PBAC advised that abaloparatide is suitable for prescribing by medical practitioners only.

7.18 The PBAC recommended that the Early Supply Rule should apply to abaloparatide. The PBAC noted that the Early Supply Rule applies to both romosozumab and teriparatide.

7.19 The PBAC noted that its recommendation was on a cost-minimisation basis and advised that, because abaloparatide is not expected to provide a substantial and clinically relevant improvement in efficacy, or reduction of toxicity, over romosozumab or teriparatide, or not expected to address a high and urgent unmet clinical need given the presence of an alternative therapy, the criteria prescribed by the *National Health (Pharmaceuticals and Vaccines – Cost Recovery) Regulations 2022* for Pricing Pathway A were not met.

7.20 The PBAC noted that this submission is not eligible for an Independent Review because it received a positive recommendation.

Outcome:
Recommended

8 Recommended listing

8.1 Add new items:

First-line initial and continuing listings

MEDICINAL PRODUCT medicinal product pack	**PBS item code**	**Max. qty packs**	**Max. qty units**	**№.of Rpts**	**Available brands**
ABALOPARATIDE					
abaloparatide, 2 mg/mL injection, 1.5 mL pen device	NEW (GE)	1	1	5	Eladynos
Restriction Summary [New 1] / Treatment of Concept: [New 1A]					

Concept ID (for internal Dept. use)	**Category / Program:** GENERAL - General Schedule (Code GE)
	Prescriber type: ☒ Medical Practitioners
	Restriction type: ☒ Authority Required: Telephone/Electronic
	Administrative Advice:

	Applications for authorisation under this restriction may be made in real time using the Online PBS Authorities system (see www.servicesaustralia.gov.au/HPOS) or by telephone by contacting Services Australia on 1800 888 333.
	Administrative Advice: No increase in the maximum quantity or number of units may be authorised.
	Administrative Advice: No increase in the maximum number of repeats may be authorised.
	Indication: Severe established osteoporosis
	Treatment Phase: Initial treatment - First-line therapy
	Treatment criteria:
	Must be treated by a consultant physician
	Clinical criteria:
	Patient must not have received PBS-subsidised treatment with any of, (i) anti-resorptive therapy, (ii) teriparatide, (iii) romosozumab, or (iv) abaloparatide,
	OR
	Patient must have developed intolerance to romosozumab of a severity necessitating permanent treatment withdrawal within the first 6 months of therapy.
	AND
	Clinical criteria:
	Patient must be at very high risk of fracture
	AND
	Clinical criteria:
	Patient must have a Bone Mineral Density (BMD) T-score of -2.5 or less
	AND
	Clinical criteria:
	Patient must have had a symptomatic fracture due to minimal trauma
	AND
	Clinical criteria:
	Patient must have had at least 1 hip or symptomatic vertebral fracture in the previous 24 months; or
	Patient must have had at least 2 fractures including 1 symptomatic new fracture in the previous 24 months
	AND
	Clinical criteria:
	The treatment must be the sole PBS-subsidised therapy for this condition
	AND
	Clinical criteria:
	The treatment must not exceed a lifetime maximum of 18 months of PBS and non-PBS-subsidised therapy with this drug for this condition
	Prescribing Instructions: Details of fracture history including the date(s), site(s), the symptoms associated with the fracture(s) and the score of the qualifying BMD measurement must be provided at the time of application.
	Prescribing Instructions: A vertebral fracture is defined as a 20% or greater reduction in height of the anterior or mid portion of a vertebral body relative to the posterior height of that body, or, a 20% or greater reduction in any of these heights compared to the vertebral body above or below the affected vertebral body.

	Prescribing Instructions: Anti-resorptive therapies for osteoporosis include alendronate sodium, risedronate sodium, raloxifene hydrochloride, denosumab and zoledronic acid.
Restriction Summary [New 2] / Treatment of Concept: [2A]	
Concept ID (for internal Dept. use)	**Category / Program:** GENERAL - General Schedule (Code GE)
	Prescriber type: ☒Medical Practitioners
	Restriction type: ☒ Authority Required: Telephone/Electronic
	Administrative Advice: Applications for authorisation under this restriction may be made in real time using the Online PBS Authorities system (see www.servicesaustralia.gov.au/HPOS) or by telephone by contacting Services Australia on 1800 888 333.
	Administrative Advice: No increase in the maximum quantity or number of units may be authorised.
	Administrative Advice: No increase in the maximum number of repeats may be authorised.
	Indication: Severe established osteoporosis
	Treatment Phase: Continuing treatment - First-line therapy
	Treatment criteria:
	Must be treated by a medical practitioner identifying as either: (i) a consultant physician, (ii) a general practitioner
	Clinical criteria:
	Patient must have previously received PBS-subsidised treatment with this drug for this condition as first-line therapy
	AND
	Clinical criteria:
	The treatment must be the sole PBS-subsidised therapy for this condition
	AND
	Clinical criteria:
	The treatment must not exceed a lifetime maximum of 18 months of PBS and non-PBS-subsidised therapy with this drug for this condition

Second-line initial and continuing listings

MEDICINAL PRODUCT medicinal product pack	PBS item code	Max. qty packs	Max. qty units	№.of Rpts	Available brands
ABALOPARATIDE					
abaloparatide, 2 mg/mL injection, 1.5 mL pen device	NEW (GE)	1	1	5	Eladynos
Restriction Summary [New 3] / Treatment of Concept: [New 3A]					

Concept ID	**Category / Program:** GENERAL - General Schedule (Code GE)
	Prescriber type: ☒Medical Practitioners
	Restriction type: ☒ Authority Required: Telephone/Electronic

(for internal Dept. use)	
	Administrative Advice: Applications for authorisation under this restriction may be made in real time using the Online PBS Authorities system (see www.servicesaustralia.gov.au/HPOS) or by telephone by contacting Services Australia on 1800 888 333.
	Administrative Advice: No increase in the maximum quantity or number of units may be authorised.
	Administrative Advice: No increase in the maximum number of repeats may be authorised.
	Indication: Severe established osteoporosis
	Treatment Phase: Initial treatment - Second-line therapy
	Treatment criteria:
	Must be treated by a consultant physician
	Clinical criteria:
	Patient must not have received PBS-subsidised treatment with any of, (i) teriparatide, (ii) romosozumab or (iii) abaloparatide,
	OR
	Patient must have developed intolerance to (i) teriparatide, or (ii) romosozumab of a severity necessitating permanent treatment withdrawal within the first 6 months of therapy.
	AND
	Clinical criteria:
	Patient must be at very high risk of fracture
	AND
	Clinical criteria:
	Patient must have a Bone Mineral Density (BMD) T-score of -3.0 or less
	AND
	Clinical criteria:
	Patient must have 2 or more fractures due to minimal trauma
	AND
	Clinical criteria:
	Patient must have experienced at least 1 symptomatic new fracture after at least 12 months continuous therapy with an anti-resorptive agent at adequate doses
	AND
	Clinical criteria:
	The treatment must be the sole PBS-subsidised therapy for this condition
	AND
	Clinical criteria:
	The treatment must not exceed a lifetime maximum of 18 months of PBS and non-PBS-subsidised therapy with this drug for this condition
	Prescribing Instructions: A vertebral fracture is defined as a 20% or greater reduction in height of the anterior or mid portion of a vertebral body relative to the posterior height of that body, or, a 20% or greater reduction in any of these heights compared to the vertebral body above or below the affected vertebral body.
	Prescribing Instructions:

	If treatment with anti-resorptive therapy is contraindicated according to the relevant TGA-approved Product Information, details of the contraindication must be documented in the patient's medical record at the time treatment with this drug is initiated.
	Prescribing Instructions: If an intolerance of a severity necessitating permanent treatment withdrawal develops during the relevant period of use of one anti-resorptive agent, alternate anti-resorptive agents must be trialled so that the patient achieves the minimum requirement of 12 months continuous therapy. Details must be documented in the patient's medical record at the time treatment with this drug is initiated.
	Prescribing Instructions: Anti-resorptive therapies for osteoporosis and their adequate doses which will be accepted for the purposes of administering this restriction are alendronate sodium 10 mg per day or 70 mg once weekly, risedronate sodium 5 mg per day or 35 mg once weekly or 150 mg once monthly, raloxifene hydrochloride 60 mg per day (women only), denosumab 60 mg once every 6 months and zoledronic acid 5 mg per annum.
	Prescribing Instructions: Details of prior anti-resorptive therapy, fracture history including the date(s), site(s), the symptoms associated with the fracture(s) which developed after at least 12 months continuous anti-resorptive therapy and the score of the qualifying BMD measurement must be provided at the time of application.
Restriction Summary [New 4] / Treatment of Concept: [4A]	
Concept ID (for internal Dept. use)	**Category / Program:** GENERAL - General Schedule (Code GE)
	Prescriber type: ☒ Medical Practitioners
	Restriction type: ☒ Authority Required: Telephone/Electronic
	Administrative Advice: Applications for authorisation under this restriction may be made in real time using the Online PBS Authorities system (see www.servicesaustralia.gov.au/HPOS) or by telephone by contacting Services Australia on 1800 888 333.
	Administrative Advice: No increase in the maximum quantity or number of units may be authorised.
	Administrative Advice: No increase in the maximum number of repeats may be authorised.
	Indication: Severe established osteoporosis
	Treatment Phase: Continuing treatment - Second-line therapy
	Treatment criteria:
	Must be treated by a medical practitioner identifying as either: (i) a consultant physician, (ii) a general practitioner
	Clinical criteria:
	Patient must have previously received PBS-subsidised treatment with this drug for this condition as second-line therapy
	AND
	Clinical criteria:
	The treatment must not exceed a lifetime maximum of 18 months of PBS and non-PBS-subsidised therapy with this drug for this condition

8.2 Flow-on changes:

Flow-on changes will be required to the first-line listing for romosozumab and to the second-line listings for teriparatide and romosozumab listings to note that a patient must not have received prior treatment with abaloparatide.

First-line listings

14641N / romosozumab – replace clinical criterion 32822 with NEW CC1.1 and add NEW CC1.2:

	Clinical criteria:
	Patient must not have received PBS-subsidised treatment with any of: (i) anti-resorptive therapy, (ii) teriparatide, (iii) romosozumab, (iv) abaloparatide;
	OR
	Patient must have developed intolerance to abaloparatide of a severity necessitating permanent treatment withdrawal within the first 6 months of therapy.

Second-line listings

14093R / teriparatide – replace clinical criterion 28168 with:

	Clinical criteria:
	Patient must not have received PBS-subsidised treatment with any of: (i) romosozumab, (ii) abaloparatide;
	OR
	Patient must have developed intolerance to (i) romosozumab, or (ii) abaloparatide of a severity necessitating permanent treatment withdrawal within the first 6 months of therapy.

12301K / romosozumab – replace clinical criterion 28161 and 26970 with:

	Clinical criteria:
	Patient must not have received PBS-subsidised treatment with any of: (i) teriparatide, (ii) (abaloparatide), or (iii) romosozumab;
	OR
	Patient must have developed intolerance to (i) teriparatide, or (ii) abaloparatide of a severity necessitating permanent treatment withdrawal within the first 6 months of therapy.

These restrictions may be subject to further review. Should there be any changes made to the restrictions the sponsor will be informed.

9 Context for Decision

The PBAC helps decide whether and, if so, how medicines should be subsidised through the Pharmaceutical Benefits Scheme (PBS) in Australia. It considers applications regarding the listing of medicines on the PBS and provides advice about other matters relating to the operation of the PBS in this context. A PBAC decision in

relation to PBS listings does not necessarily represent a final PBAC view about the merits of the medicine or the circumstances in which it should be made available through the PBS. The PBAC welcomes applications containing new information at any time.

10 Sponsor's Comment

Theramex continues to work with the Department to make Eladynos available to patients. The listing of Eladynos will offer patients greater choice of treatment.