



Australian Government

Department of Health and Aged Care

Therapeutic Goods Administration

Australian Public Assessment Report for Jubbonti/Wyost

Active ingredient/s: Denosumab

Sponsor: Sandoz Pty Ltd

October 2024

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- The Therapeutic Goods Administration (TGA) is part of the Australian Government Department of Health and Aged Care and is responsible for regulating therapeutic goods, including medicines, medical devices, and biologicals.
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List of abbreviations

Abbreviation	Meaning
ADA	Anti-drug antibodies
AE	Adverse events
ARGPM	Australian Regulatory Guidelines for Prescription Medicines
ARTG	Australian Register of Therapeutic Goods
AUC	Area under the concentration-time curve
AUC _{0-last}	Area under the curve from time 0 to the last quantifiable sample
AUC _{inf}	Area under the curve from time 0 extrapolated to infinite time
AUEC	area under the effect-time curve
BMD	Bone mineral density
C _{avg}	Average concentration
CI	Confidence intervals
CfB	change from baseline
C _{max}	The maximum concentration that a drug attains in a specified compartment
CTX	Carboxy-terminal crosslinked telopeptides of type I collagen
EMA	European Medicines Agency
FAS	Full analysis set
FDA	Food and Drug Administration (United States of America)
GMR	Geometric mean ratio
Nab	Neutralising antibody
PD	Pharmacodynamics
PI	Product Information
PK	Pharmacokinetics
PINP	Procollagen I N-terminal pro-peptide
RANKL	Receptor Activator of Nuclear factor Kappa beta (RANK) Ligand
SD	Standard deviation
t _{1/2}	Half life
TEAE	Treatment emergent adverse event(s)
TGA	Therapeutic Goods Administration
TP1	Treatment period 1
TP2	Treatment period 2

Jubbonti/Wyost (denosumab) submission

Type of submission:	New biological entity (Biosimilar)
Product name:	Jubbonti (biosimilar of Prolia) /Wyost (biosimilar of Xgeva)
Active ingredient:	Denosumab
Decision:	Approved
Approved therapeutic use for the current submission:	<p>Wyost:</p> <p><i>Prevention of skeletal related events in patients with multiple myeloma and in patients with bone metastases from solid tumours.</i></p> <p><i>Treatment of giant cell tumour of bone in adults or skeletally mature adolescents that is recurrent, or unresectable, or resectable but associated with severe morbidity.</i></p> <p><i>Treatment of hypercalcaemia of malignancy that is refractory to intravenous bisphosphonate.</i></p> <p>Jubbonti:</p> <p><i>The treatment of osteoporosis in postmenopausal women. Jubbonti significantly reduces the risk of vertebral, non-vertebral and hip fractures.</i></p> <p><i>Treatment to increase bone mass in men with osteopaenia receiving androgen deprivation therapy for non-metastatic prostate cancer (see section 5.1 of the PI: Pharmacodynamic properties, Clinical trials).</i></p> <p><i>Treatment to increase bone mass in men with osteoporosis at increased risk of fracture.</i></p> <p><i>Treatment to increase bone mass in women and men at increased risk of fracture due to long-term systemic glucocorticoid therapy.</i></p>
Date of decision:	7 August 2024
Date of entry onto ARTG:	23 August 2024
ARTG number:	Wyost: 418514 ; Jubbonti: 418515
Sponsor's details:	Sandoz Pty Ltd 100 Pacific Highway, North Sydney, NSW 2060
Dose form:	Jubbonti/Wyost: sterile, for injection at pH approx. 5.2
Strength:	<p>Jubbonti: Each 1 mL single-use pre-filled syringe contains 60 mg denosumab.</p> <p>Wyost: Each vial contains a deliverable dose of 120 mg denosumab in 1.7 mL of solution (70 mg/mL).</p>
Container:	Jubbonti: Pre-filled syringe is made from type I glass with stainless steel 29-gauge needle with safety guard (The pre-

filled syringe with automatic needle guard is not made with natural rubber latex).

Wyost: single use vial (type I glass) with stopper (fluoropolymer coated elastomeric) and seal (aluminium) with flip-off cap.

Pack size: **Jubbonti:** One pre-filled syringe, presented in blister packaging

Wyost: One vial

Route of administration: solution for injection

Dosage: **Jubbonti:** 60 mg, once every 6 months.

Wyost: 120 mg administered as a single subcutaneous injection once every 4 weeks into the thigh, abdomen or upper arm.

For further information regarding dosage, such as dosage modifications to manage adverse reactions, refer to the Product Information.

Pregnancy category: **Jubbonti/Wyost:** Category D

Drugs which have caused, are suspected to have caused or may be expected to cause, an increased incidence of human fetal malformations or irreversible damage. These drugs may also have adverse pharmacological effects.

The use of any medicine during pregnancy requires careful consideration of both risks and benefits by the treating health professional. The [pregnancy database](#) must not be used as the sole basis of decision making in the use of medicines during pregnancy. The TGA does not provide advice on the use of medicines in pregnancy for specific cases. More information is available from [obstetric drug information services](#) in your state or territory.

Jubbonti/Wyost (denosumab) – proposed indication

Denosumab is a human IgG2 monoclonal antibody antagonist that targets the Receptor Activator of Nuclear factor Kappa beta (RANK) Ligand (RANKL). Denosumab prevents RANKL-mediated, osteoclast activation, thereby reducing the breakdown of bone (the RANKL-RANK interaction regulates osteoclast formation, activation and survival)¹.

This AusPAR describes the evaluation of the submission by Sandoz Pty Ltd (the Sponsor) to register the biosimilar products, Jubbonti and Wyost (both denosumab, which are identical to the reference products, Prolia and Xgeva, respectively), for the following proposed indications:

Jubbonti (Prolia):

- *The treatment of osteoporosis in postmenopausal women. Prolia significantly reduces the risk of vertebral, non-vertebral and hip fractures.*

¹ Dore RK. The RANKL pathway and denosumab. *Rheum Dis Clin North Am.* 2011 Aug;37(3):433-52, vi-vii. doi: 10.1016/j.rdc.2011.07.004. PMID: 22023901.

- *Treatment to increase bone mass in men with osteopaenia receiving androgen deprivation therapy for non-metastatic prostate cancer.*
- *Treatment to increase bone mass in men with osteoporosis at increased risk of fracture.*
- *Treatment to increase bone mass in women and men at increased risk of fracture due to long-term systemic glucocorticoid therapy.*

Wyost (Xgeva):

- *Prevention of skeletal related events in patients with multiple myeloma and in patients with bone metastases from solid tumours.*
- *Treatment of giant cell tumour of bone in adults or skeletally mature adolescents that is recurrent, or unresectable, or resectable but associated with severe morbidity.*
- *Treatment of hypercalcaemia of malignancy that is refractory to intravenous bisphosphonate.*

Osteoporosis and other bone-related disorders

Denosumab, a bone anti-resorptive medication, is used to treat several conditions related to bone health including:

- Osteoporosis
- Osteopenia
- Bone metastases in multiple myeloma
- Giant cell tumour of bone
- Hypercalcaemia of malignancy.

Osteoporosis/osteopenia

Osteoporosis is loss of bone mineralisation and deterioration of bone micro-architecture². This leads to decreased bone strength and increase in fracture risk. Subclinical vertebral fractures lead to loss of height and vertebral deformities. Non-vertebral fractures usually present following a fall. Risk factors include increasing age, menopause, immobility and long-term treatment with glucocorticoids.

Bone mineral density (BMD) can be measured by dual energy X-ray absorptiometry (DXA) and expressed as a T-score (the number of standard deviations from the mean value). Normal BMD is a T-score ≥ -0.1 (not more than 1.0 SD below young adult mean). Osteopenia is a T-score < -0.1 and > -2.5 (between 1.0 and 2.5 SD below young adult mean). Osteoporosis is a T-score ≤ -2.5 (2.5 SD or more below young adult mean).

As stated in RACGP 2017: “Approximately 3% of men and 13% of women in Australia 50–69 years of age are osteoporotic, rising to 13% and 43% for men and women older than 70 years of age. Fifty-five per cent of men and 49% of women between 50 and 69 years of age are osteopenic, with similar prevalences in the over-70 years age group. It is estimated that by 2022 approximately 72% of women and 62% of men older than 50 years of age will have osteoporosis or osteopenia, according to WHO criteria.”

² The Royal Australian College of General Practitioners and Osteoporosis Australia. Osteoporosis prevention, diagnosis and management in postmenopausal women and men over 50 years of age. 2nd edn. East Melbourne, Vic: RACGP, 2017

Multiple myeloma

Multiple myeloma is a type of blood cancer arising from plasma cells in the bone marrow³. Plasma cells are found only in the bone marrow and not usually in circulating blood. Plasma cells are derived from B lymphocytes in the bone marrow. Plasma cells develop from B lymphocytes in response to infection whereupon they make antibodies to eradicate/neutralise the pathogen.

In 2022, it was estimated that 2,625 new cases of multiple myeloma would be diagnosed in Australia (1,540 males and 1,085 females). In 2022, it was estimated that a person had a 1 in 111 (or 0.90%) risk of being diagnosed with multiple myeloma by the age of 85 (1 in 94 or 1.1% for males and 1 in 135 or 0.74% for females). In multiple myeloma, the tumour forms multiple lytic lesions in bone. This can result in bone pain, fractures and hypercalcaemia⁴.

Giant cell tumour of bone

Giant cell tumour of bone is a benign bone tumour, representing 4-10% of all primary bone tumours and 15-20% of all benign bone tumours⁵. It occurs in young adults 20 to 40 years of age, has a high recurrence rate and a potential for aggressive behaviour, and up to 5% metastasize. It is most commonly located in the metaphysis or at the epiphysis of femur or tibia. It consists of a combination of osteoblasts, monocytes and giant cells (which are of osteoclast origin). The tumours are destructive of the surrounding bone. RANKL is involved in the pathogenesis of the tumour.

Hypercalcaemia of malignancy

Hypercalcaemia of malignancy occurs when the serum calcium, corrected for albumin, is elevated beyond 2.6 mmol/L or >upper limit of normal for the reference laboratory⁶. It is a medical emergency and should be treated aggressively. Treatment should be commenced in symptomatic patients or when serum calcium is >3.0 mmol/L. It is due to increased osteoclastic breakdown of bone in malignancies such as multiple myeloma, or tumours that secrete parathyroid-related protein or calcitriol.

Regulatory status

Australian regulatory status

This product is considered a new biosimilar medicine for Australian regulatory purposes.

International regulatory status

At the time the TGA considered this submission, a similar submission had been considered by other regulatory agencies. Table 1 summarises these submissions.

³ Myeloma. Cancer Council, 2023. <https://cancer.org.au/cancer-information/types-of-cancer/myeloma>

⁴ Cancer Australia. Multiple myeloma in Australia statistics. January 2024. <https://www.canceraustralia.gov.au/cancer-types/myeloma/statistics#:~:text=In%202022%2C%20it%20is%20estimated,or%200.74%25%20for%20females>

⁵ Hosseinzadeh S, Tiwari V, De Jesus O. Giant Cell Tumor (Osteoclastoma) [Updated 2024 Jan 31]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2024 Jan-. Available from: <https://www.ncbi.nlm.nih.gov/books/NBK559229/>

⁶ Cancer Institute NSW. Hypercalcaemia of Malignancy (HCM). 15th December 2022. [https://www.eviq.org.au/clinical-resources/oncological-emergencies/486-hypercalcaemia-of-malignancy-hcm#:~:text=Hypercalcaemia%20of%20malignancy%20\(HCM\)%20is,value%20used%20in%20a%20lab](https://www.eviq.org.au/clinical-resources/oncological-emergencies/486-hypercalcaemia-of-malignancy-hcm#:~:text=Hypercalcaemia%20of%20malignancy%20(HCM)%20is,value%20used%20in%20a%20lab).

Table 1: International regulatory status

Region	Biosimilar	Submission date	Approval date
EU	Jubbonti	25 April 2023	CHMP opinion: 22 March 2024 EC adoption: 16 May 202
	Wyost	25 April 2023	CHMP opinion: 22 March 2024 EC adoption: 17 May 2024
US	Jubbonti	5 December 2022	5 March 2024
	Wyost	5 December 2022	5 March 2024
Canada	Jubbonti	27 January 2023	16 February 2024
	Wyost	27 January 2023	1 March 2024

*CHMP: Committee for Medicinal Products for Human Use (CHMP) of the European Medicines Agency

Registration timeline

Table 2 captures the key steps and dates for this submission.

This submission was evaluated under the [standard prescription medicines registration process](#).

Table 2: Timeline for the Jubbonti/Wyost submission (PM-2023-03741-1-5)

Description	Date
Submission dossier accepted and first round evaluation commenced	3 October 2023
Evaluation completed	31 May 2024
Delegate's ⁷ Overall benefit-risk assessment	2 July 2024
Registration decision (Outcome)	7 August 2024
Registration in the ARTG	23 August 2024
Number of working days from submission dossier acceptance to registration decision*	214

*Statutory timeframe for standard submissions is 255 working days

Evaluation overview

Relevant guidelines or guidance documents referred to by the Delegate are listed below:

⁷ The 'Delegate' is the Delegate of the Secretary of the Department of Health and Aged Care who made the final decision to either include the new medicine/indication on the ARTG or reject the submission, under section 25 of the Therapeutic Goods Act

- Biosimilar medicines regulation, Version 2.2, April 2018.
<https://www.tga.gov.au/resources/resource/guidance/biosimilar-medicines-regulation>
- International scientific guideline: Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: non-clinical and clinical issues. EMEA/CHMP/BMWP/42832/2005 Rev1 adopted by the TGA.
<https://www.tga.gov.au/resources/resource/international-scientific-guidelines/international-scientific-guideline-guideline-similar-biological-medicinal-products-containing-biotechnology-derived-proteins-active-substance-non-clinical-and-clinical-issues>
- International scientific guideline: Guideline on immunogenicity assessment of biotechnology-derived therapeutic proteins. EMEA/CHMP/BMWP/14327/2006 adopted by the TGA. <https://www.tga.gov.au/resources/resource/international-scientific-guidelines/international-scientific-guideline-guideline-immunogenicity-assessment-biotechnology-derived-therapeutic-proteins>
- International scientific guideline: Guideline on the evaluation of medicinal products in the treatment of primary osteoporosis. CPMP/EWP/552/95 Rev. 2 adopted by the TGA.
<https://www.tga.gov.au/resources/resource/international-scientific-guidelines/international-scientific-guideline-guideline-evaluation-medicinal-products-treatment-primary-osteoporosis>

Quality evaluation summary

Comparison of critical quality attributes (including but not limited to primary, secondary and tertiary structure and product-related variants, molecular size variants, higher order structure, drug product related quality attributes, process impurity profile and biological characteristics, and potency) were conducted to demonstrate biosimilar comparability to the reference products. These studies demonstrated a high similarity between the biosimilar products and the innovator products across most critical quality attributes. The only exception was the higher mannose N-glycan levels occasionally present in biosimilar drug substance lots. The Sponsor complied with a request to monitor mannose content in DS lots.

The Sponsor also demonstrated a satisfactory production process with appropriate in-process controls and identification of critical manufacturing steps within the manufacturing process, consistency of medicine manufacture verified by process validation and demonstrated through batch analysis, validation of analytical procedures utilised to assess drug specifications and control of product sterility and of infectious disease & adventitious agents. The container closure systems chosen are appropriate and compatible with the product and product labelling conforms to Therapeutic Goods Order 91.

The quality Evaluator concluded that the Sponsor satisfactorily demonstrated comparability between Jubbonti/Wyost drug products and the reference products Prolia and Xgeva. The submitted quality data indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

From a quality perspective, compliance with the relevant section of the Therapeutic Goods Act, relevant Therapeutic Goods Orders and the [Prescription Medicines Collection guidelines](#) (formerly the Australian Regulatory Guidelines for Prescription Medicines (ARGPM)) has been demonstrated.

Nonclinical (toxicology) evaluation summary

No new nonclinical data or further nonclinical evaluation were required for this submission. Previously submitted and evaluated nonclinical data satisfactorily address nonclinical aspects of safety and efficacy relating to this submission.

Clinical evaluation summary

Summary of clinical studies

The clinical dossier contains two studies:

- Study CGP24112101: a Phase I, pharmacokinetics (PK), pharmacodynamics (PD), safety and immunogenicity study in healthy male volunteers.
- Study CGP24112301: a Phase I/III, PK, PD, efficacy, safety and immunogenicity study in postmenopausal women with osteoporosis.

Pharmacology

Pharmacokinetics

Bioequivalence to relevant registered products

Study CGP24112101 assessed the bioequivalence of denosumab (Jubbonti/Wyost) with EU-approved denosumab (Xgeva) (Xgeva-EU) and US-approved denosumab (Xgeva) (Xgeva-US) in healthy adult males. Denosumab was administered as a single dose of 35 mg subcutaneously. The PK variables were AUC_{last} , AUC_{inf} , C_{max} , $AUC_{\%extrap}$, T_{max} , λz (estimate of the terminal elimination rate constant) and $t_{1/2}$.

Bioequivalence was demonstrated by AUC_{last} , AUC_{inf} , and C_{max} as the 90% confidence intervals (CIs) for the ratio test/reference were all between 0.80 and 1.25. The geometric mean ratio (GMR) (90% CI) denosumab (Jubbonti/Wyost)/Xgeva-EU was 1.09 (1.03 to 1.16) for AUC_{inf} and 1.02 (0.97 to 1.08) for C_{max} . The GMR (90% CI) denosumab (Jubbonti/Wyost)/Xgeva-US was 1.06 (1.00 to 1.13) for AUC_{inf} and 1.00 (0.95 to 1.06) for C_{max} . The plasma concentration profiles overlapped. The PK parameters were all similar. For denosumab (Jubbonti/Wyost) mean (SD) C_{max} was 3050 (892) ng/mL and $t_{1/2}$ was 16.3 (5.54) days. Median (range) T_{max} was 9.99 (2.96 to 32.0) days.

Study CGP24112301 assessed the bioequivalence between denosumab (Jubbonti/Wyost) with EU-Prolia at a dose of 60 mg subcutaneously in postmenopausal women with osteoporosis. The 90% CI for the GMR for AUC_{inf} and C_{max} for denosumab concentrations were within the bounds for bioequivalence. AUC_{inf} was 366000 day•ng/mL for denosumab (Jubbonti/Wyost) and 369000 day•ng/mL for EU-Prolia: GMR (90% CI) denosumab (Jubbonti/Wyost)/ EU-Prolia 0.99 (0.93 to 1.05). C_{max} was 6910 ng/mL for denosumab (Jubbonti/Wyost) and 7120 ng/mL for EU-Prolia: GMR (90% CI) denosumab (Jubbonti/Wyost)/ EU-Prolia 0.97 (0.92 to 1.03).

The clinical Evaluator concluded that Jubbonti/Wyost fulfils the PK requirements as a biosimilar for Xgeva and Prolia. Bioequivalence was demonstrated in the following two contexts:

- denosumab (Jubbonti/Wyost) with EU approved denosumab (Xgeva) (Xgeva-EU) and US approved denosumab (Xgeva) (Xgeva-US) at a dose of 35 mg in healthy adult males.

- denosumab (Jubbonti/Wyost) with EU approved denosumab (Prolia) (EU-Prolia) at a dose of 60 mg subcutaneously in postmenopausal women with osteoporosis.

Pharmacodynamics

Study CGP24112101 compared the PD of denosumab (Jubbonti/Wyost) with EU-approved denosumab (Xgeva) (Xgeva-EU) and US-approved denosumab (Xgeva) (Xgeva-US) in healthy adult males. The treatments were administered as a single dose of 35 mg subcutaneously. The PD outcome measures were serum CTX (Carboxy-terminal crosslinked telopeptides of type I collagen; a measure of bone turnover) and PINP (Procollagen I N-terminal pro-peptide; a bone formation marker that is indicative of type I collagen disposition). The PD variables were area under the effect-time curve (AUEC) and rebound area.

Equivalent effects were demonstrated for CTX as the 90% CIs and 95% CIs for the ratios of geometric means for AUEC of % change from baseline (CfB) in serum CTX were within the bounds of 0.8 and 1.25. The time profile of %CfB in CTX was similar for the three treatment groups. The time profile of %CfB in PINP was similar for the three treatment groups. AUEC was similar for the three treatment groups but rebound area was less for the denosumab (Jubbonti/Wyost) group.

Study CGP24112301 compared the PD effects of denosumab (Jubbonti/Wyost) with EU-Prolia at a dose of 60 mg subcutaneously in postmenopausal women with osteoporosis. The PD outcome measures were CTX and PINP (Procollagen I N-terminal pro-peptide). The 95% CI and 90% CI for the GMR for AUEC of %CfB in CTX were within the bounds for equivalence for the FDA, the EU and the PMDA. The adjusted geometric mean AUEC change from baseline to Week 52 in CTX was 15800 %•day for denosumab (Jubbonti/Wyost) and 15800 %•day for EU-Prolia: GMR (95% CI) denosumab (Jubbonti/Wyost)/ EU-Prolia 1.00 (0.98 to 1.01). GMR (90% CI) denosumab (Jubbonti/Wyost)/ EU-Prolia 1.00 (0.98 to 1.01). The profiles of % change from baseline in CTX over time were similar for the two treatments. The profiles of % change from baseline in PINP over time were similar for the two treatments.

The Clinical Evaluator is of the view that denosumab (Jubbonti/Wyost) fulfils the PD requirements as a biosimilar for denosumab (Xgeva) and denosumab (Prolia). Equivalent effects on CTX and PINP were demonstrated in the following two contexts:

- denosumab (Jubbonti/Wyost) with EU approved denosumab (Xgeva) (Xgeva-EU) and US approved denosumab (Xgeva) (Xgeva-US) at a dose of 35 mg in healthy adult males.
- denosumab (Jubbonti/Wyost) with EU approved denosumab (Prolia) (EU-Prolia) at a dose of 60 mg subcutaneously in postmenopausal women with osteoporosis.

Clinical efficacy

There was a single, pivotal efficacy study, study CGP24112301: a Phase I/III, PK, PD, efficacy, safety and immunogenicity study in postmenopausal women with osteoporosis (PMO).

Study CGP24112301 was a randomised, double-blind, integrated Phase I/III study in postmenopausal women with osteoporosis to compare the PK, PD, efficacy, safety and immunogenicity of denosumab (Jubbonti/Wyost) with denosumab -Prolia, EU authorised (Prolia-EU). This was an international, multicenter, randomised, double-blind, two-arm, parallel-group study with a total duration of up to 83 weeks. The study comprised a screening period of up to 5 weeks to assess a subject's eligibility and two treatment periods: TP1 (Day 1 to Week 52) and TP2 (Week 52 to Week 78).

Approximately 492 women with PMO were planned to be randomised on Day 1 in a 1:1 ratio to receive either two 60 mg s.c. doses of denosumab (Jubbonti/Wyost) or EU-Prolia during TP1. At

Week 52, subjects in the latter group were re-randomised 1:1 to either continue with a third dose of EU-Prolia or switch to denosumab (Jubbonti/Wyost) for TP2.

The study treatments were:

1. denosumab -Jubbonti/Wyost
2. denosumab -Prolia, EU authorised (Prolia-EU).

The treatments were administered as a dose of 60 mg in 1 mL, by subcutaneous injection. Each participant was scheduled to receive three doses at 26-week intervals.

If a participant developed hypercalcaemia or hypocalcaemia during the study, the Investigator could use his/her medical judgement and reduce the calcium and/or vitamin D supplementation respectively give appropriate additional supplementation to maintain serum calcium concentration within normal range.

The primary efficacy outcome measure was the % change from baseline in lumbar spine (LS) BMD (%CfB of LS-BMD) at Week 52. Equivalence was defined as the 95% CI for the difference in means being within the bounds of -1.45% to 1.45%.

The secondary endpoints were:

- AUEC of %CfB in serum CTX after first dose. Equivalence was defined as the 95% CI for the ratio of geometric means being within the bounds of 0.80 to 1.25.
- AUC_{inf} for denosumab plasma concentrations. Equivalence was defined as the 90% CI for the ratio of geometric means being within the bounds of 0.80 to 1.25.
- C_{max} for denosumab plasma concentrations. Equivalence was defined as the 90% CI for the ratio of geometric means being within the bounds of 0.80 to 1.25.
- LS-BMD, femoral neck BMD (FN-BMD), femur BMD (TH-BMD) at Week 26, Week 52 and Week 78.
- CTX and PINP concentrations.

The safety endpoints were: Adverse events (AEs), injection site reactions, fractures, antidrug antibodies (ADA) and neutralising antibodies.

Randomisation was conducted by Interactive Response Technology (IRT) in the ratio 1:1, and stratified by region (US, Rest of World, and Japan), age group (<65 years / ≥65 years), prior bisphosphonate use (yes/no) and body weight group (<70 kg / ≥70 kg).

Following treatment period 1 (TP1) (52 weeks), the subjects in the EU-Prolia group were re-randomised to either continuing EU-Prolia or switching to denosumab (Jubbonti/Wyost) in a 1:1 ratio for the third dose of study treatment. The TP1 full analysis set (FAS) included all subjects who were randomised into TP1, who received at least one dose of study drug and for whom at least one post-baseline LS-BMD value (either at Week 26 or Week 52 or at both visits) was available. Subjects in this analysis set were analysed according to their intended (randomised) treatment and stratification.

The primary efficacy analysis used a mixed model for repeated measures. This included, as covariates, prior bisphosphonate use, DXA machine type and baseline LS-BMD. Missing post-baseline BMD was assumed to be missing at random within the model.

There were 1158 subjects screened and 527 were randomised to treatment: 263 to denosumab (Jubbonti/Wyost) and 264 to EU-Prolia. All randomised subjects received treatment in TP1. There were 253 (96.2%) subjects in the denosumab (Jubbonti/Wyost) group and 249 (94.3%) in the EU-Prolia who completed TP1. One subject in the denosumab (Jubbonti/Wyost) group

died. One (0.4%) subject in the denosumab (Jubbonti/Wyost) group and three (1.1%) in the EU-Prolia discontinued due to AE.

In TP2, there were 253 subjects in the denosumab (Jubbonti/Wyost) group who continued, a further 124 from the EU Prolia group were randomised to denosumab (Jubbonti/Wyost) and 125 continued with EU-Prolia. Two subjects in the EU-Prolia group discontinued during TP2.

There were no subjects excluded from the FAS dataset for protocol deviations. The most frequent protocol deviation leading to exclusion from the PD dataset was missing observations.

All the study subjects were female, and the age range was 55 to 80 years. There were 126 (47.9%) subjects in the denosumab (Jubbonti/Wyost) group and 125 (47.3%) in the EU-Prolia aged ≥ 65 years. There were 54 (20.5%) subjects in the denosumab (Jubbonti/Wyost) group and 55 (20.8%) in the EU-Prolia weighing ≥ 70 kg.

The treatment groups were similar in baseline disease characteristics. There were 49 (18.6%) subjects in the denosumab (Jubbonti/Wyost) group and 51 (19.3%) in the EU-Prolia with prior bisphosphonate use. Prior treatment for osteoporosis was similar for the two treatment groups.

In TP1, in the denosumab (Jubbonti/Wyost) group, 255 (97.0%) subjects received two doses of study medication and eight (3.0%) received one dose; in the EU-Prolia group 255 (96.6%) subjects received two doses of study medication and nine (3.4%) received one dose. All the subjects included in TP2 received one dose.

Results for the primary efficacy outcome

The 95% CI for the difference in %CfB in LS-BMD was within the bounds for equivalence for both the FDA and the PMDA. The adjusted mean change (SE) from baseline to Week 52 in LS-BMD was 4.963 (0.2630) % for denosumab (Jubbonti/Wyost) and 5.140 (0.2627) % for EU-Prolia: difference (95% CI) denosumab (Jubbonti/Wyost) – EU-Prolia -0.177 (-0.830 to 0.475).

Results for other efficacy outcomes

The 95% CI and 90% CI for the GMR for AUEC of %CfB in CTX were within the bounds for equivalence for the FDA, the EU and the PMDA. The adjusted geometric mean AUEC change from baseline to Week 52 in CTX was 15800 %•day for denosumab (Jubbonti/Wyost) and 15800 %•day for EU-Prolia: GMR (95% CI) denosumab (Jubbonti/Wyost)/EU-Prolia 1.00 (0.98 to 1.01); GMR (90% CI) denosumab (Jubbonti/Wyost)/ EU-Prolia 1.00 (0.98 to 1.01).

The 90% CI for the GMR for AUC_{inf} and C_{max} for denosumab concentrations were within the bounds for bioequivalence. AUC_{inf} was 366000 day•ng/mL for denosumab (Jubbonti/Wyost) and 369000 day•ng/mL for EU-Prolia: GMR (95% CI) denosumab (Jubbonti/Wyost) / EU-Prolia 0.99 (0.93 to 1.05). C_{max} was 6910 ng/mL for denosumab (Jubbonti/Wyost) and 7120 ng/mL for EU-Prolia: GMR (95% CI) denosumab (Jubbonti/Wyost) / EU-Prolia 0.97 (0.92 to 1.03).

The mean (SD) change from baseline to Week 26 in LS-BMD was 3.5877 (3.73579) % for denosumab (Jubbonti/Wyost) and 3.7144 (3.89730) % for EU-Prolia. The mean (SD) change from baseline to Week 78 in LS-BMD was 6.8222 (3.95225) % for denosumab (Jubbonti/Wyost)/denosumab (Jubbonti/Wyost), 7.0694 (4.72955) for EU-Prolia/EU-Prolia and 6.4212 (4.47102) % for EU-Prolia/denosumab (Jubbonti/Wyost).

The mean (SD) change from baseline to Week 26 in FH-BMD was 2.0343 (3.43682) % for denosumab (Jubbonti/Wyost) and 1.8210 (3.11073) % for EU-Prolia; and from baseline to Week 52 in FH-BMD was 2.3401 (3.69145) % for denosumab (Jubbonti/Wyost) and 2.6465 (3.29726) % for EU-Prolia. The mean (SD) change from baseline to Week 78 in FH-BMD was 3.2220 (4.03733) % for denosumab (Jubbonti/Wyost)/denosumab (Jubbonti/Wyost), 2.9406 (3.92115) for EU-Prolia/EU-Prolia and 2.6857 (3.64193) % for EU-Prolia/denosumab (Jubbonti/Wyost).

The mean (SD) change from baseline to Week 26 in TH-BMD was 0.7577 (0.08931) % for denosumab (Jubbonti/Wyost) and 0.7678 (0.08583) % for EU-Prolia; and from baseline to Week 52 in TH-BMD was 3.2882 (2.70260) % for denosumab (Jubbonti/Wyost) and 3.2234 (2.64633) % for EU-Prolia. The mean (SD) change from baseline to Week 78 in TH-BMD was 3.7037 (3.28071) % for denosumab (Jubbonti/Wyost)/denosumab (Jubbonti/Wyost), 4.0898 (2.96530) for EU-Prolia/EU-Prolia and 3.9987 (3.33311) % for EU-Prolia/denosumab (Jubbonti/Wyost).

The profiles of % change from baseline in CTX over time were similar for the two treatments. The profiles of % change from baseline in PINP over time were similar for the two treatments. The denosumab plasma concentration time profiles were similar for the two treatments.

Clinical safety

There were no pivotal studies that assessed safety as the sole primary outcome.

There was one pivotal efficacy study:

- Study CGP24112301: a Phase I/III, PK, PD, efficacy, safety and immunogenicity study in postmenopausal women with osteoporosis.

The safety endpoints were: AEs, injection site reactions, fractures, antidrug antibodies (ADA) and neutralising antibodies (NAb).

There was one clinical pharmacology study:

- Study CGP24112101: a Phase I, PK, PD, safety and immunogenicity study in healthy male volunteers.

The safety outcome measures were AEs, clinical laboratory tests, ECGs, ADAs and NAb.

Denosumab (Jubbonti/Wyost) has a similar safety profile to EU-Prolia. The rates and profiles of TEAEs were similar for the two products. The most common TEAE was hypocalcaemia, which is consistent with the known mechanism of action for denosumab. There were few deaths and serious adverse events, and these were not attributable to study treatment.

Immunogenicity was similar for the two products. There were few patients with ADA titres in either treatment group: in Study CGP24112301 TP1 there were two (0.8%) subjects in the denosumab (Jubbonti/Wyost) group and two (0.8%) in the EU-Prolia which is in line with published immunogenicity rates (Prolia US PI and SmPC) of Prolia (<1%) and the incidence of NAb was very low. Vast majority of the positive ADA results were transient, i.e. most subjects with a positive ADA results tested negative again at the following assessment. Hence, denosumab demonstrated low immunogenicity in the clinical data. The incidence of ADAs was higher compared with historical studies of the originator drug, which can be explained by the highly sensitive assays that were applied in this study. The switch from EU-Prolia to the proposed biosimilar denosumab (Jubbonti/Wyost) in TP2 did not result in increased immunogenicity or adverse events indicative of hypersensitivity reactions.

In Study CGP24112301: there were four hip fractures reported in the denosumab (Jubbonti/Wyost) group and none in the EU-Prolia. However, the rate of vertebral fractures was similar for the two treatment groups. During the study new vertebral fractures were reported in 15 (5.7%) subjects in the denosumab (Jubbonti/Wyost) group and 24 (9.1%) in the EU-Prolia. Overall, the rate of fractures was not significantly greater in the denosumab (Jubbonti/Wyost) group.

The safety data from Study CGP24112101 were supportive of safety for denosumab (Jubbonti/Wyost), but these data have limitations. The dose used in Study CGP24112101 was 35 mg, which is significantly less than the proposed dosing of denosumab (Jubbonti/Wyost).

Also, the subjects in this study were healthy males and not representative of the target population. Hence Study CGP24112101 may not be suitable for demonstrating the safety profile in clinical practice.

Risk Management Plan (RMP) evaluation

The Sponsor has been granted a waiver for submitting a RMP on the grounds that “there are no additional risk minimisation measures in place for the reference product that this biosimilar has demonstrable bioequivalence to.”

Risk-benefit analysis

Study CPG24112301 was designed to demonstrate similar efficacy, PD and PK between denosumab (Jubbonti/Wyost) with the reference product denosumab (Prolia). The sample size calculation was powered to demonstrate all three outcomes. The primary efficacy outcome measure, LS-BMD, was an acceptable surrogate efficacy outcome measure for osteoporosis clinical trials. The study population was postmenopausal women with osteoporosis, which corresponds with one of the proposed indications for Jubbonti. The dosing and administration corresponded with that for Jubbonti. The randomisation, blinding and statistical analysis were satisfactory.

Similar efficacy was demonstrated within the predefined limits. Equivalence was defined as the 95% CI for the difference in means being within the bounds of -1.45% to 1.45%. was within the bounds for equivalence for both the FDA and the PMDA. The difference (95% CI), denosumab (Jubbonti/Wyost) – EU-Prolia, in %CfB in LS-BMD was -0.177 (-0.830 to 0.475). The secondary efficacy outcome measures were supportive, and there were no conflicting results.

The submitted study has demonstrated similar efficacy for denosumab (Jubbonti/Wyost) with the reference product denosumab (Prolia), for the indication of:

- The treatment of osteoporosis in postmenopausal women. Jubbonti significantly reduces the risk of vertebral, non-vertebral and hip fractures.

In comparison with EU-Prolia, denosumab (Jubbonti/Wyost) was demonstrated to have equivalent efficacy, bioequivalence and equivalent pharmacodynamic effect.

- For efficacy, the difference (95% CI), denosumab (Jubbonti/Wyost) – EU-Prolia, in %CfB in LS-BMD was -0.177 (-0.830 to 0.475), which was well within the predefined bounds of -1.45% to 1.45%.
- Bioequivalence was demonstrated in comparison with EU approved denosumab (Xgeva) (Xgeva-EU), US approved denosumab (Xgeva) (Xgeva-US) and EU approved denosumab (Prolia) (EU-Prolia).
- Equivalent pharmacodynamic effect (for CTX) was demonstrated in comparison with EU approved denosumab (Xgeva) (Xgeva-EU), US-approved denosumab (Xgeva) (Xgeva-US) and EU approved denosumab (Prolia) (EU-Prolia).

With regard to the other indications, the Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: non-clinical and clinical issues. EMEA/CHMP/BMWP/42832/2005 states:

“When biosimilar comparability has been demonstrated in one indication, extrapolation of clinical data to other indications of the reference product could be acceptable, but needs to be scientifically justified. In case it is unclear whether the safety and efficacy confirmed in

one indication would be relevant for another indication, additional data will be required. Extrapolation should be considered in the light of the totality of data, i.e. quality, non-clinical and clinical data. It is expected that the safety and efficacy can be extrapolated when biosimilar comparability has been demonstrated by thorough physico-chemical and structural analyses as well as by in vitro functional tests complemented with clinical data (efficacy and safety and/or PK/PD data) in one therapeutic indication. Additional data are required in certain situations, such as

1. the active substance of the reference product interacts with several receptors that may have a different impact in the tested and non-tested therapeutic indications
2. the active substance itself has more than one active site and the sites may have a different impact in different therapeutic indications
3. the studied therapeutic indication is not relevant for the others in terms of efficacy or safety, i.e. is not sensitive for differences in all relevant aspects of efficacy and safety.”

Denosumab has only one receptor target (RANKL) and only one active site. All the approved indications for the reference product have the same underlying mode of action and treatment rationale. The Clinical Evaluator is of the view that the studied therapeutic indication is relevant for all the other approved therapeutic indications.

The delegate agrees that it is acceptable to extrapolate efficacy to all the approved indications of the reference products for the following reasons:

- denosumab has only one receptor target (RANKL) and only one active site.
- All the approved indications for the reference product have the same underlying mode of action and treatment rationale.
- The studied therapeutic indication is relevant for all the other approved therapeutic indications.

Denosumab (Jubbonti/Wyost) has a similar safety profile to EU-Prolia. The rates of TEAEs and the profile were similar for the two products. The most common TEAE was hypocalcaemia, which is consistent with the known mechanism of action for denosumab. There was 1 death and few serious adverse events, and these were not attributable to study treatment.

Immunogenicity was similar for the two products. There were few patients with ADA titres in either treatment group: in Study CGP24112301 TP1 there were two (0.8%) subjects in the denosumab (Jubbonti/Wyost) group and two (0.8%) in the EU-Prolia. The incidence of NAbs was very low and vast majority of the positive ADA results were transient.

The delegate agrees that denosumab (Jubbonti/Wyost) has a favourable benefit-risk balance, and denosumab (Jubbonti/Wyost) has equivalent efficacy, bioequivalence and equivalent pharmacodynamic effect to the reference products, denosumab (Prolia), AUST R 159323, and denosumab (Xgeva), AUST R 175041. The safety profile of denosumab (Jubbonti/Wyost) was similar to the reference products.

Outcome

The delegate has no objection to the approval of denosumab (Jubbonti/Wyost), for the indications:

Jubbonti:

- *The treatment of osteoporosis in postmenopausal women. Jubbonti significantly reduces the risk of vertebral, non-vertebral and hip fractures.*
- *Treatment to increase bone mass in men with osteopaenia receiving androgen deprivation therapy for non-metastatic prostate cancer (see section 5.1 Pharmacodynamic properties, Clinical trials).*
- *Treatment to increase bone mass in men with osteoporosis at increased risk of fracture.*
- *Treatment to increase bone mass in women and men at increased risk of fracture due to long-term systemic glucocorticoid therapy.*

Wyost:

- *Prevention of skeletal related events in patients with multiple myeloma and in patients with bone metastases from solid tumours.*
- *Treatment of giant cell tumour of bone in adults or skeletally mature adolescents that is recurrent, or unresectable, or resectable but associated with severe morbidity.*
- *Treatment of hypercalcaemia of malignancy that is refractory to intravenous bisphosphonate.*

Specific conditions of registration applying to these goods

Laboratory testing & compliance with Certified Product Details (CPD)

All batches of JUBBONTI and WYOST (denosumab) supplied in Australia must comply with the product details and specifications approved during evaluation and detailed in the Certified Product Details (CPD).

When requested by the TGA, the Sponsor should be prepared to provide product samples, specified reference materials and documentary evidence to enable the TGA to conduct laboratory testing on the Product. Outcomes of laboratory testing are published biannually in the TGA Database of Laboratory Testing Results <http://www.tga.gov.au/ws-labs-index> and periodically in testing reports on the TGA website.

Certified Product Details

The Certified Product Details (CPD), as described in Guidance 7: Certified Product. Details of the Prescription medicines collection (formerly the Australian Regulatory Guidelines for Prescription Medicines (ARGPM)) for the above products should be provided upon registration of these therapeutic goods. In addition, an updated CPD should be provided when changes to finished product specifications and test methods are approved in a Category 3 application or notified through a self-assessable change.

Attachment 1 and 2. Product Information

The [Product Information \(PI\)](#) approved with the submission for Jubbonti/Wyost which is described in this AusPAR can be found as Attachment 1 and 2. It may have been superseded. For the most recent PI and [Consumer Medicines Information \(CMI\)](#), please refer to the TGA [PI/CMI search facility](#).

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Reference/Publication #