Australian Government
Department of Health and Aged Care
Therapeutic Goods Administration

Australian Public Assessment Report for Eladynos

Active ingredient: Abaloparatide

Sponsor: Theramex Australia Pty Ltd

February 2025

About the Therapeutic Goods Administration (TGA)

- 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.
- The TGA administers the *Therapeutic Goods Act 1989* (the Act), applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety, and efficacy.
- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to the Australian public outweigh any risks associated with the use of therapeutic goods.
- The TGA relies on the public, healthcare professionals and industry to report problems with therapeutic goods. The TGA investigates reports received to determine any necessary regulatory action.
- To report a problem with a therapeutic good, please see the information on the TGA website.

About AusPARs

- The Australian Public Assessment Report (AusPAR) provides information about the evaluation of a prescription medicine and the considerations that led the TGA to approve or not approve a prescription medicine submission. Further information can be found in Australian Public Assessment Report (AusPAR) guidance.
- AusPARs are prepared and published by the TGA.
- AusPARs are static documents that provide information that relates to a submission at a particular point in time. The publication of an AusPAR is an important part of the transparency of the TGA's decision-making process.
- A new AusPAR may be provided to reflect changes to indications or major variations to a prescription medicine subject to evaluation by the TGA.

Contents

List of abbreviations

Abbreviation	Meaning
ADA	anti-drug antibodies
ACM	Advisory Committee on Medicines
ACV	Advisory Committee on Vaccines
ARTG	Australian Register of Therapeutic Goods
ASA	Australia specific annex
AUC0-inf	area under the concentration time curve extrapolated to infinity
BMD	bone mineral density
BMI	body mass index
bpm	beats per minute
BSA	body surface area
CER	clinical evaluation report
CHMP	Committee on Human Medicinal Products
CI	confidence interval
CL	clearance
C_{max}	maximum concentration
CMI	consumer medicines information
COR	comparable overseas regulator
CP	centralised procedure
CrCL	creatinine clearance
DLP	Data lock point
ECG	electrocardiogram
EMA	European Medicines Agency
EU	European Union
FDA	Food and Drug Administration
GCP	Good Clinical Practice
hPTH	human parathyroid hormone
hPTHrP(1-34)	human parathyroid hormone-related peptide (1-34)
IDV	Integrated Dataverse
ITT	intent-to-treat
IV	intravenous
LLOQ	lower limit of quantification
MAA	Marketing Authorisation Application

Abbreviation	Meaning
MACE	major adverse cardiovascular event
MAH	Marketing Authorisation Holder
miTT	modified intent-to-treat
NAb	neutralising antibody
PI	product information
PK	pharmacokinetic(s)
PopPK	population pharmacokinetics
PRAC	Pharmacovigilance Risk Assessment Committee
PS	propensity score
PSUR	periodic safety update report
PTH	parathyroid hormone
PTHR1	parathyroid hormone receptor 1
PTHrP	parathyroid hormone-related peptide
RMP	Risk management plan
SC	subcutaneous
SD	standard deviation
SmPC	Summary of Product Characteristics
SOC	system organ class
$t_{½}$	elimination half-life
TEAE	treatment emergent adverse event
TGA	Therapeutic Goods Administration
t_{max}	time to maximum concentration
US	United States of America
Vss	distribution volume at steady state

Product submission

Submission details

Type of submission:	New chemical entity
Product name:	Eladynos
Active ingredient:	Abaloparatide
Decision:	Approved
Date of decision:	6 November 2024
Date of entry onto ARTG:	28 November 2024
ARTG number:	430937
▼*Black Triangle Scheme:*	Yes
	This product is to be included in the Black Triangle Scheme. The PI and CMI for Eladynos must include the black triangle symbol and mandatory accompanying text for 5 years, which starts from the date the product is first supplied in Australia.
Sponsor's name and address:	Theramex Australia Pty Ltd
	Level 22, 60 Margaret Street, Sydney NSW, Australia, 2000
Dose form:	Solution for injection
Strength:	Each dose (40 microlitres) contains 80 micrograms of abaloparatide
Container:	Cartridge in a prefilled pen
Pack size:	Each pre-filled pen contains 1.5 mL of solution (30 doses).
	Eladynos is supplied in a pack size of 1 or 3 pre-filled pens. A starter pack containing 1 prefilled pen may also be supplied. No needles are supplied with the medicinal product.
Approved therapeutic use for the current submission:	Eladynos is indicated for the treatment of osteoporosis in postmenopausal women at increased risk of fracture.
Route of administration:	Subcutaneous injection
Dosage:	80 micrograms once daily; approximately the same time each day. The maximum total duration of treatment should be 18 months.
	For further information regarding dosage, such as dosage modifications to manage adverse reactions, refer to the Product Information.
Pregnancy category:	Pregnancy Category B3

Eladynos is contraindicated during pregnancy and in women of childbearing potential. Eladynos is not to be used in women who are, or may be, pregnant.

For further information on the use of Eladynos (such as dosage, pregnancy category, contraindications, and precautions etc.) refer to the Product Information (PI) document or contact a doctor or pharmacist. Use the TGA PI/CMI search facility to view the current Product Information (PI) and Consumer Medicines Information (CMI).

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.

Product background

This AusPAR describes the submission by Theramex Australia to register Eladynos - abaloparatide 2 mg/mL solution for injection cartridge in a prefilled pen- for the following proposed indication:

For the treatment of osteoporosis in postmenopausal women at increased risk of fracture.

Disease or condition

Osteoporosis is a common condition marked by reduced bone strength, leading to an increased risk of fragility fractures, especially in the spine, forearm, and hip. In 2020-21, 889,400 (3.6%) Australians of all ages had been diagnosed with osteoporosis, with higher incidence among females (females 5.9%, males 1.1%). Osteoporosis is more common in older age groups, increasing from 5.6% of people aged 55-64 years to 20.1% of people aged 75 years and over. Osteoporosis is often undiagnosed, until a person presents with a fracture. Fractures can result in chronic pain and reduced mobility. Hip fractures, particularly, are associated with higher mortality rates.

The most dangerous fractures are those requiring surgery, such as hip fractures, which are linked to serious risks, permanent disability, and increased mortality. Radiological vertebral fractures are common in postmenopausal women, with about 60% being asymptomatic. Symptomatic vertebral fractures cause acute pain and reduced mobility for about a month. Radiological vertebral fractures are key indicators of osteoporosis severity, and Bone Mineral Density (BMD) is used as a surrogate marker for this condition, as defined by WHO criteria.

Current treatment options

Existing treatments for osteoporosis are categorized into, (1) those that decrease bone loss and (2) those that increase bone mineral density (BMD) and build new bone, as described below.

1. Antiresorptive therapy: This approach aims to decrease bone loss. It includes drugs like oestrogens, selective oestrogen receptor modulators, anti-RANK ligand antibodies, and bisphosphonates. These agents work by inhibiting the bone-resorbing activity of osteoclasts.
2. Bone anabolic therapy: This approach focuses on increasing new bone formation and bone mineral density (BMD). Drugs like teriparatide stimulate the production and activity of osteoblasts, which are responsible for building new bone.

Both approaches are designed to strengthen bones and reduce the likelihood of fractures. Abaloparatide falls into the latter category (2).

Clinical rationale

The efficacy of abaloparatide for the proposed indication was primarily demonstrated in a single pivotal study (BA058-05-003). Over an 18-month treatment period, abaloparatide showed a statistically significant reduction in the incidence of new vertebral fractures compared to the placebo. Additionally, abaloparatide significantly increased BMD at the lumbar spine, hip, and femoral neck compared to placebo. However, while there was a trend towards a reduction in the incidence of non-vertebral fractures in those who received abaloparatide compared to the placebo, this was not statistically significant. When compared to teriparatide, which was used as an open-label active comparator, abaloparatide demonstrated comparable findings regarding fracture endpoints, with slightly more favourable improvements in BMD at the hip and femoral neck. These endpoints, such as BMD and serum bone markers, serve as supportive surrogates. They do not independently establish the effects of abaloparatide and therefore do not allow for a definitive conclusion on its efficacy compared to teriparatide.

According to EMA guidelines on osteoporosis, the efficacy of a new anti-osteoporotic drug should be demonstrated for both vertebral and non-vertebral fractures, preferably in separate, adequately powered studies. The clinical program for abaloparatide included only a single randomized controlled study (BA058-05-003) that examined the incidence of new fractures as a primary endpoint. This study was limited by Good Clinical Practice (GCP) deficiencies at two study sites, leading to their exclusion and a significant decrease in the overall study population by 16%. Additionally, efficacy in reducing non-vertebral fractures could not be established for abaloparatide in this study.

Despite this, the EMA Assessor noted that there was no scientific reason to presume efficacy would be confined to vertebral fractures and not extend to non-vertebral fractures, regardless of statistical significance. This is further supported by the comparative efficacy of abaloparatide and teriparatide in both the pivotal study BA058-05-003 and the retrospective cohort study BA058-05-028, which compared the two treatments in the prevention of non-vertebral fractures in propensity score-matched cohorts. Results from other efficacy endpoints generally supported the primary finding of a reduction in the risk of osteoporotic fractures with abaloparatide.

Hypercalcaemia and hypercalciuria were less common in patients treated with abaloparatide compared to those on teriparatide, but more frequent than in those on the placebo. The product information for abaloparatide includes similar precautions for hypercalcemia as those for teriparatide.

Pharmacodynamic evaluation of abaloparatide was undertaken in seven Phase 1 studies, two Phase 2 studies, and three Phase 3 studies. The studies evaluated in the COR reports primarily examined abaloparatide effects on bone turnover markers and bone remodelling.

Regulatory status

Australian regulatory status

This product is considered a new chemical entity for Australian regulatory purposes.

International regulatory status

A similar application for Eladynos was submitted to the EU by the MAH, Radius International Ltd on 29 October 2021. The MAA was approved by the EMA via the Centralised Procedure (CP) on 12 December 2022. The accepted therapeutic indication was identical to that being proposed in this application. It is noted that a previous MAA was submitted through the CP by Radius International Ltd for the same product in November 2015. The CHMP ultimately recommended against market authorisation of the product on 26 July 2018 on the basis of a negative benefit-risk assessment at the time. The current MAA for Eladynos was not a re-submission or re-evaluation of the previous application but did incorporate evaluation reports from the 2015 MAA as points of reference. It also included new clinical data from additional interventional and observational studies, as well as post-marketing data obtained from the US market since 28 April 2017.

An application for Tymlos (abaloparatide) was submitted to the US FDA on 30 March 2016 and approved by the US FDA on 28 April 2017. The accepted indications were different to that proposed in this application and were listed for the '*treatment of postmenopausal women with osteoporosis at high risk for fracture or patients who have failed or are intolerant to other available osteoporosis therapy'* and *'treatment to increase bone density in men with osteoporosis at high risk for fracture or patients who have failed or are intolerant to other available osteoporosis therapy'*.

This application was submitted through the TGA's Comparable Overseas Regulator (COR-B) process, using evaluation reports from EMA as the comparable overseas regulator. The full dossier was submitted to the TGA.

At the time the TGA considered this submission, the European Union had approved an identical submission on 12 December 2022. A similar submission was approved in the US on 28 April 2017 with broader indications being approved.

The COR assessment documents and reports included met the Therapeutic Goods Administration (TGA) requirements for COR report-based applications, where the COR is the EMA. This evaluation is based on the COR assessment reports in Module 1.11.4. The studies in Module 5 were not independently reviewed by the Evaluator, but Module 5 clinical study reports and Module 2 clinical summaries were referenced as needed for clarity on points in the COR assessment reports.

In the COR reports, it was noted that the Sponsor claimed all clinical studies were conducted according to GCP. However, the EMA Assessor identified serious GCP-related issues in the pivotal study BA058-05-003, leading to the exclusion of two study sites (Sites 131 and 132). This reduced the original study population by 16%, from 2463 to 2070 subjects. The COR assessment reports are based on this smaller subset of participants.

A waiver was granted for the paediatric population (from birth to under 18 years) for subcutaneous abaloparatide, in accordance with Regulation (EC) No 1901/2006, due to potential safety concerns in this group. This waiver is considered acceptable from a clinical perspective.

The following table summarises these submissions and provides the indications where approved.

Table 1: International regulatory status

Region	Submission date	Status	Approved indications
European Union	29 October 2021.	Approved on 12 December 2022.	Eladynos is indicated for *'the treatment of osteoporosis in postmenopausal women at increased risk of fracture'*. Eladynos is provided as a colourless, clear solution of injection in a pre-filled pen. It is administered subcutaneously at a dosage of 80 micrograms once daily to the lower abdomen area. Originally submitted to the EU by the MAH, Radius International Ltd.
United States of America	TYMLOS (Abaloparatide) 30 March 2016	Approved on 28 April 2017	TYMLOS (Abaloparatide) is indicated for the "*treatment of postmenopausal women with osteoporosis at high risk for fracture or patients who have failed or are intolerant to other available osteoporosis therapy"* and *"treatment to increase bone density in men with osteoporosis at high risk for fracture or patients who have failed or are intolerant to other available osteoporosis therapy"*.
European Union	November 2015	Denied market authorisation on 26 July 2018	The CHMP ultimately recommended against market authorisation of the product on 26 July 2018 on the basis of a negative benefit-risk assessment at the time.

Registration timeline

The following table captures the key steps and dates for this submission.

This submission was evaluated under the standard prescription medicines registration process.

Table 2: Timeline for Submission PM-2023-05942-1-5

Description	Date
Submission dossier accepted and first round evaluation commenced	January 2024
First round evaluation completed	April - May 2024
Sponsor provides responses on questions raised in first round evaluation	July 2024
Second round evaluation completed	August 2024
Delegate's[1] Overall benefit-risk assessment	October 2024
Registration decision (outcome)	November 2024
Administrative activities and registration in the ARTG completed	November 2024
Number of working days from submission dossier acceptance to registration decision*	150

*Statutory timeframe for standard submissions is 255 working days

* The COR-A process has a 120 working day evaluation and decision timeframe.

* The COR-B process has a 175 working day evaluation and decision timeframe.

Submission overview and risk/benefit assessment

Quality evaluation summary

Abaloparatide is a chemically synthesised analogue of the first 34 amino acid residues of human parathyroid hormone related peptide [hPTHrP(1–34)] (displaying 76% homology). It also shares sequence homology with human parathyroid hormone (41% homology to hPTH(1–34) [= teriparatide]). The drug acts as a parathyroid hormone receptor 1 (PTHR1) agonist.

Approval is recommended from a quality perspective. The drug product formulation used in the Phase 3 clinical studies is the same as the product formulation proposed for registration.

The Product Information is considered acceptable from a pharmaceutical quality perspective.

The labelling is considered acceptable from a pharmaceutical quality perspective.

The provisional ARTG records are finalised.

The GMP clearances for all manufacturing sites are current until 07/05/2025.

[1] 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.

Nonclinical (toxicology) evaluation summary

The application has been made under the COR-B pathway. Nonclinical evaluation is by reference to the EMA Rapporteur Day 80 Critical Assessment Report. All relevant nonclinical data have been considered.

Key findings

- Theramex Australia Pty Ltd has applied to register a new chemical entity, abaloparatide (Eladynos), proposed to be used for the treatment of osteoporosis in postmenopausal women at increased risk of fracture. Treatment is to involve subcutaneous administration of 80 µg once daily, with a maximum total duration of treatment of 18 months.
- Module 4 was of satisfactory quality and adequate in scope, consistent with ICH M3 (R2). All pivotal safety-related studies were GLP-compliant.
- Abaloparatide is a chemically synthesised analogue of the first 34 amino acid residues of human parathyroid hormone related peptide [hPTHrP(1–34)] (displaying 76% homology). It also shares sequence homology with human parathyroid hormone (41% homology to hPTH(1–34) [= teriparatide]). The drug acts as a parathyroid hormone receptor 1 (PTHR1) agonist.
- Abaloparatide was shown to possess sub nanomolar affinity for human PTHR1 in its G-protein coupled conformational state. PTHR1 agonism was demonstrated in cell-based functional experiments. Dose-dependent increases in bone mineral density with abaloparatide were shown in rat and monkey models of postmenopausal osteoporosis [ovariectomy-induced bone loss], with this accompanied by increased bone strength (at vertebral and non-vertebral sites).
- Abaloparatide was shown not to additionally act as an agonist at the human parathyroid receptor 2 (PTHR2). Screening assays revealed no clinically relevant secondary pharmacological targets for the drug.
- Safety pharmacology studies indicated no likely pharmacologically mediated adverse effects on CNS, respiratory, gastrointestinal or renal function. Abaloparatide has peripheral vasodilatory activity (PTHR1-mediated) and causes tachycardia. Abaloparatide does not inhibit hERG K+ channel current at clinically relevant concentrations.
- Absorption of abaloparatide after subcutaneous administration was rapid in laboratory animal species, as in humans. Plasma half-life was short across species. SC bioavailability was moderately low. Plasma protein binding was moderate. Rapid and wide tissue distribution of 125I-abaloparatide-derived radioactivity was demonstrated in rats, with penetration of the blood-brain barrier evident. As a peptide, abaloparatide is subject to proteolytic degradation, yielding multiple peptide fragments that are excreted renally.
- In vitro experiments revealed no CYP inhibition or induction by abaloparatide and established that the drug is not a substrate or inhibitor of major transporters. Accordingly, the potential for pharmacokinetic interactions with abaloparatide is considered to be low.
- Abaloparatide showed a low order of acute toxicity by the subcutaneous route in laboratory animal species.
- Repeat-dose toxicity studies by the SC route were conducted in rats (up to 6 months) and cynomolgus monkeys (up to 9 months). Bone, bone marrow, kidney and heart were identified as the key targets. Effects on these are mostly attributable to exaggerated pharmacology.
- Abaloparatide was negative for genotoxicity in the standard battery of tests.

- Abaloparatide was clearly carcinogenic in a 2-year study in rats, with a marked increase in the incidence of osteosarcomas observed in both sexes and at all dose levels (≥10 µg/kg/day SC; yielding only a modest multiple of the clinical exposure). Osteoblastomas were also increased. The carcinogenic activity of abaloparatide is seen to be related to primary pharmacology, and broadly similar to that of teriparatide. The clinical relevance of the rodent tumour findings is tempered by differences in bone physiology and pharmacology of humans but cannot be dismissed. Specification of a lifetime maximum treatment duration (18 months) serves as an appropriate risk mitigation strategy.
- Male fertility was unaffected by abaloparatide in rats. No other reproductive and developmental toxicity studies have been performed, justified by the indicated patient population (postmenopausal women). The risk of embryofetal harm posed by abaloparatide is expected to be comparable to that of teriparatide. As such, assignment to Pregnancy Category B3 (rather than Category D as the Sponsor proposes) is warranted.
- There are no nonclinical objections to the registration of Eladynos for the proposed indication.
- The updated Product Information document is considered to be acceptable from a nonclinical perspective.
  - The Sponsor has proposed some further revisions to the PI text on Paediatric use (Section 4.4), Effects on fertility and Use in Pregnancy (Section 4.6) and Carcinogenicity (Section 5.3), but these are acceptable. Other requested changes, including to the Pregnancy Category (=B3), have been made in full.

Clinical evaluation summary

The initial formulation of the abaloparatide was in a lyophilisate form and was examined in the first-in-human pharmacokinetic and pharmacodynamic study (2-52-52127-001) and the Phase 1 study (BA058-05-001). Later formulations (numbers 2 to 4) were in liquid form, with different concentrations of the abaloparatide (0.5, 1.0, and 2.0 mg/mL). These liquid formulations were used in the subsequent pharmacokinetic studies.

Summary of clinical studies

The pharmacokinetics of abaloparatide was examined in healthy subjects, subjects with renal impairment and in the target population of postmenopausal women with osteoporosis. This was comprised of six Phase 1 studies, one Phase 2 dose finding study, one supportive Phase 2 study, and two Phase 3 confirmatory studies, of which one was considered pivotal (study BA058-05-003). Analysis of pharmacokinetics were undertaken using non-compartmental methods.

Pharmacology

A population pharmacokinetic analysis was conducted to develop a structural model, identify significant covariates, and simulate outcomes for patients with varying degrees of renal impairment. Using non-linear mixed effect modelling, data from the pivotal Phase 3 study BA058-05-003 and six Phase 1 studies were analysed, including 5,232 measurable concentrations from 967 subjects. The final two-compartment model with linear elimination revealed limitations such as visit-dependent bioavailability and empirical time-varying infusion rates. Significant covariates included dose on bioavailability and Vc, patient factors on bioavailability, and creatinine clearance on CL. Time-constant ADAs significantly influenced pharmacokinetic parameters, though this approach was seen as a limitation. An updated

analysis with time-varying ADAs provided comparable estimates. The EMA Assessor found the overall analysis acceptable with reasonable precision in parameter estimates.

The overall pharmacokinetics of the abaloparatide were adequately described. The EMA Assessor noted that no new clinical pharmacokinetic data was submitted by the Applicant in their Marketing Authorisation Application (MAA) in 2021, compared to the previous MAA from 2015. No major significant issues regarding the data were identified during the previous MAA. The EMA Assessor concluded that "the available pharmacokinetic data are considered sufficient for the purpose of this application." The Evaluator concurs with these sentiments and the overall conclusions regarding pharmacokinetics in the COR report.

The COR report's conclusions on the primary pharmacodynamics of abaloparatide highlight its strong anabolic effects on bone and reduced bone resorption. Bone turnover markers showed dynamic changes, initially increasing and then decreasing after 12-18 months of treatment. Further reductions in these markers were observed after stopping abaloparatide and switching to alendronate, consistent with bisphosphonates' known effects. Other pharmacodynamic bone markers also aligned with abaloparatide's mechanism of action. The EMA Assessor stated that "the pharmacodynamic principles have been sufficiently described by the applicant," and the Clinical Evaluator agreed with these conclusions.

Efficacy

Pivotal Study BA058-05-003

Study BA058-05-003 was a Phase 3, multicentre, randomised, double-blind, placebo-controlled, 3-arm comparative study. It evaluated the efficacy and safety of abaloparatide compared to a placebo or teriparatide in preventing fractures in ambulatory, healthy postmenopausal women with osteoporosis. This study was followed by a 24-month extension phase (Study BA058-05-005). The treatment duration with the abaloparatide was 18 months, followed by an additional 24 months of alendronate (Study BA058-05-005), with only the first 6 months of this extension included in the original 18 months of trial data.

The inclusion criteria were representative of the target population, but the extensive exclusion criteria, as noted by the EMA Assessor, might limit the generalisability of the safety conclusions, especially for patients with a history of cardiovascular disease.

Participants were randomised in a 1:1:1 ratio to receive either 80 µg of the abaloparatide, a placebo, or 20 µg of teriparatide (the active control). The treatments with the abaloparatide and placebo were masked, while the teriparatide treatment was open-label. Both subjects and study staff were blinded to the treatment allocation. Fracture and bone mineral density (BMD) endpoints were assessed by independent third-party reviewers who were also blinded.

The EMA Assessor found the randomisation process acceptable. However, they noted that only one reviewer initially assessed patient radiographs, with a second reviewer involved only to confirm identified fractures. This might have led to an underestimation of fracture events, but it was not considered a major issue since the primary objective was to demonstrate superiority over the placebo.

The primary endpoint was the percentage of subjects with one or more incidents of new vertebral fracture from the baseline spine X-rays to post-baseline spine X-rays in patients treated with abaloparatide compared to placebo. Key secondary endpoints explored the time to first incidence of non-vertebral fractures to the follow-up visits, and percentage changes from baseline in BMD measurements of the lumbar spine, total hip and femoral neck through to the end of the 18-month treatment period with abaloparatide.

The EMA Assessor found the statistical methods generally acceptable. However, they noted that the original statistical analysis plan intended to exclude a relatively high proportion of randomised subjects (20%) from the primary efficacy analysis. Although the actual proportion of excluded subjects was lower than planned, the sensitivity analysis conducted to address this issue was deemed insufficient.

The abaloparatide met its primary efficacy endpoint, demonstrating a statistically significant reduction in the incidence of new vertebral fractures compared to placebo (0.51% vs 4.17%, p<0.0001). This corresponds to an 88% relative risk reduction (95% CI 59% to 96%) in new vertebral fractures for subjects receiving the abaloparatide versus placebo. Sensitivity analyses using multiple imputation methods on the ITT population supported the abaloparatide superiority over placebo, though with a smaller treatment effect size than observed in the primary analysis. Additional sensitivity analyses, based on different missing data patterns as requested by the EMA Assessor, generally supported the primary analysis conclusions, albeit with smaller effect sizes.

The abaloparatide prolonged the time to the first incidence of non-vertebral fractures compared to placebo, but this difference was not statistically significant (log-rank p=0.37). There was a 26% reduction in the hazard of non-vertebral fractures for subjects receiving the abaloparatide versus placebo (hazard ratio 0.74, 95% CI 0.38 to 1.43). The comparison of time to first incidence of non-vertebral fractures between the abaloparatide and teriparatide was also not statistically significant (p=0.49).

Both the abaloparatide and teriparatide significantly increased bone mineral density (BMD) at the lumbar spine, total hip, and femoral neck from baseline to 18 months compared to placebo. There was a small but statistically significant difference favouring the abaloparatide over teriparatide for BMD increases at the total hip (3.3% vs 3.0%) and femoral neck (2.7% vs 2.3%).

Subgroup analyses were consistent with the primary analysis, generally favouring the abaloparatide over placebo. Post-hoc analyses for several fracture endpoint combinations, which were not pre-specified, also generally supported the lower number and time to first incidence of fractures in the abaloparatide group compared to placebo.

Study BA058-05-005

Study BA058-05-005 was an open-label extension to study BA058-05-003 which aimed to collect clinical data from subjects who transitioned to treatment with alendronate. Following the completion of 18 months of treatment with abaloparatide or placebo in study BA058-05-003, subjects were commenced on oral alendronate 70mg once weekly for a period of 6 months. Following this, subjects continued to receive alendronate for a further 18 months (to make up to 24 months that comprised study BA058-05-005). Comparison with teriparatide was not studied in study BA058-05-005.

The endpoints for study BA058-05-005 were identical to that of study BA058-05-003.

During the 24 months of study BA-58-05-005, there were an additional 2 vertebral fractures in the previously treated abaloparatide group vs 10 new vertebral fractures in the previously assigned placebo group. The relative risk reduction in the abaloparatide group compared to placebo at Month 43 was similar to that seen at Month 18 (84% relative risk reduction, 95% CI 53% to 94%; p<0.0001).

During the 24 months of study BA-58-05-005, there were 8 new non-vertebral fractures in the previously treated abaloparatide group vs 10 new non-vertebral fractures in the previously assigned placebo group. At Month 43, the abaloparatide/alendronate group continued to have a prolonged time to first incidence of non-vertebral fractures and reduced the risk of non-

vertebral fractures when compared to placebo/alendronate. However, this was not considered statistically significant (p=0.088).

BMD continued to increase in both the abaloparatide and placebo groups, following transition to alendronate in study BA-58-05-005, with the size of the improvement in BMD at the lumbar spine, femoral neck and total hip significantly favouring the abaloparatide/alendronate group over the placebo/alendronate group at all timepoints (p<0.0001). There was also a statistically significant difference in the proportion of subjects who achieved a clinically significant improvement in BMD >3% from baseline to Month 43 that favoured the abaloparatide/ alendronate group over the placebo/alendronate group (59% vs 23%, respectively; p<0.0001).

Study ITM-058-301

Study ITM-058-301 was a Phase 3, multicentre, randomised, double-blind, 2-arm, placebo-controlled, parallel group study in Japanese subjects with osteoporosis who were a high risk of fracture. The study included 213 male and postmenopausal female subjects with primary osteoporosis who were randomised in a 2:1 ratio to receive abaloparatide or placebo over 18 months. Demographic and baseline characteristics were comparable between treatment groups. Approximately 10% of all subjects were male. The mean age of subjects was 68.7 years, with 21.8% of all subjects aged <65 years.

The primary endpoint was percent change in lumbar spine (L1-L4) BMD at the last visit. Secondary efficacy endpoints examined the percentage change from baseline in lumbar spine and hip BMD at other timepoints, incidence of new fractures, changes in bone metabolism marks and evaluation of quality of life. Primary efficacy analysis was tested sequentially using a closed testing procedure to maintain the two-sided significance level of 0.05, first in the entire population followed by the subset of patients with postmenopausal osteoporosis. Primary efficacy analysis was undertaken with an ANCOVA model that was applied to percent changes in the lumbar spine (L1-L4) BMD at the last visit from the baseline test values.

This study was initially presented by the sponsor as a confirmatory Phase 3 study. The EMA Assessor disputed this on the basis of a relatively small sample size and the choice of primary efficacy endpoint. BMD was only considered as an appropriate endpoint in exploratory studies and was determined an appropriate surrogate for fracture reduction in confirmatory studies.

The overall results from Study ITM-058-301 aligned with those from the pivotal study BA058-05-003. There were too few fractures in both treatment groups to draw meaningful conclusions regarding efficacy of treatment on fracture reduction.

Study BA058-05-028

A retrospective observational cohort study which evaluated the effectiveness and cardiovascular safety of abaloparatide in postmenopausal women who were new to anabolic therapies (abaloparatide or teriparatide). The study used anonymised patients claims data from PRA's Symphony Health Patient Source Integrated Dataverse (IDV) database for the period from 01 May 2012 to 31 January 2021. Notwithstanding limitations in aspect of the study design of the retrospective observational study BA058-05-028, the main conclusions from the study supported comparative effectiveness of abaloparatide with teriparatide in the US population.

Efficacy conclusion

Overall, the EMA and TGA clinical assessors determined that based on the totality of evidence provided, the efficacy of abaloparatide could be considered sufficiently demonstrated for the applied indication. The clinical delegate agrees with this conclusion.

Safety

A total of 1,039 postmenopausal women with osteoporosis were treated with abaloparatide across prospective clinical studies, including 694 women in the pivotal study BA058-05-003. The retrospective observational study BA058-05-028 provided safety data from 11,027 postmenopausal women exposed to abaloparatide in the US. The duration of treatment exposure to abaloparatide was considered adequate for evaluating safety data.

There was a higher incidence of treatment-emergent adverse events (TEAEs) in subjects who received abaloparatide compared to those who received teriparatide and the placebo. Patients treated with abaloparatide experienced higher rates of orthostatic hypotension, palpitations, nausea, dizziness, and headache. Additionally, a higher proportion of subjects in the abaloparatide group discontinued treatment due to these TEAEs compared to the teriparatide and placebo groups.

In study BA058-05-003, a higher percentage of subjects in the abaloparatide group experienced increases in heart rate from pre-dose to post-dose compared to the teriparatide and placebo groups. This was corroborated by the QT/QTc study (BA058-05-012), which observed an increase in heart rate in healthy subjects up to 12 hours following a single injection of 80 μg of abaloparatide, with heart rate peaking between 15 to 30 minutes post-dose.

The EMA Assessor and TGA clinical Evaluator noted a potential higher risk associated with increased heart rate and orthostatic hypotension in vulnerable patients treated with abaloparatide. The exclusion criteria in study BA058-05-003, which excluded subjects with chronic or recurrent cardiovascular disease, limit the generalisability of the safety conclusions. The higher number of withdrawals in the abaloparatide group due to palpitations, dizziness, and nausea may have led to an underestimation of cardiovascular events reported in this group over the study period. The TGA clinical delegate concurs with these observations.

However, the overall data did not confirm an association between increased heart rate with abaloparatide treatment and serious cardiovascular events. Across the clinical studies, there was no significant increased risk of major adverse cardiovascular events in subjects treated with abaloparatide compared to those treated with teriparatide or placebo. The retrospective observational study BA058-05-028 did not provide additional insights into the cardiovascular safety of abaloparatide. Post-marketing surveillance did not identify any new safety signals related to cardiovascular events with abaloparatide treatment. Although teriparatide, a similar class product, also showed an increase in heart rate (albeit to a lesser extent) in study BA058-05-003, post-market experience since its authorisation in 2003 has not noted any concerning cardiovascular safety signals.

Overall, the TGA clinical Evaluator found abaloparatide to be generally well tolerated with an acceptable safety profile. There are uncertainties regarding the clinical relevance of transient increases in heart rate on the risk of serious cardiovascular events, particularly in populations with a history of chronic cardiovascular disease. These uncertainties have been largely mitigated with modifications in the EU Summary of Product Characteristics (SmPC) and Safety Concerns in the Risk Management Plan (RMP), which acknowledge the potential risk of major cardiovascular events. The TGA clinical Evaluator considers the Summary of Safety Concerns in the EU RMP and the precautions in the SmPC to sufficiently characterise the risks identified during the COR evaluation procedure.

Recommendation following the clinical evaluation

The quality, nonclinical, RMP and clinical Evaluators have all recommended approval. The clinical delegate considers that sufficient data and justification have been provided to approve

abaloparatide (pre-filled pen contains 3 mg of abaloparatide in 1.5 mL of solution - corresponding to 2 mg per mL) solution, for registration with the following indication:

'Eladynos is indicated for the treatment of osteoporosis in postmenopausal women at increased risk of fracture.'

Risk management plan

The summary of safety concerns and their associated risk monitoring and mitigation strategies are summarised in Table 3. The TGA may request an updated RMP at any stage of a product's life cycle, during both the pre-approval and post-approval phases.

Table 3: Summary of safety concerns

Summary of safety concerns		Pharmacovigilance		Risk minimisation	
		Routine	Additional	Routine	Additional
Important identified risks	None	–	–	–	–
Important potential risks	Osteosarcoma	✓*	–	✓	–
	Serious cardiovascular events (i.e. MACE, arrythmia)	✓	✓†	✓	–
Missing information	None	–	–	–	–

* Follow-up questionnaire, † EU PASS

The RMP Evaluator recommended conditions of registration relating to the versions of the risk management plan, requirement for periodic safety update reports, and inclusion of the medicine in the Black Triangle Scheme.

- The safety concerns in the ASA are consistent with the safety concerns listed in the EU-RMP and comparable to similar product teriparatide. The summary of safety concerns is considered acceptable from an RMP perspective.
- The sponsor has proposed routine pharmacovigilance for all safety concerns. Routine pharmacovigilance includes a specific adverse reaction follow-up questionnaire for osteosarcoma. Additional pharmacovigilance includes an EU Post-Authorisation Safety Study (PASS) to further evaluate the risk of serious cardiovascular events (i.e. MACE, arrhythmias). The pharmacovigilance plan in the ASA aligns with that in the EU-RMP and is acceptable from an RMP perspective.
- Only routine risk minimisation measures have been proposed. The risk minimisation plan is considered acceptable from an RMP perspective. The sponsor has provided adequate justification for not implementing a Patient Consent Form to address the risk of osteosarcoma for abaloparatide, based on current evidence. The sponsor will provide an evaluation of global safety data for osteosarcoma through routine PSUR reporting which will monitor adequacy of risk minimisation measures.

- The PI will be provided with the product as a package insert as required for all injectable products not administered by a healthcare professional. The sponsor updated the PI to include instructions for use (IFU). To improve readability of PI, the sponsor should consider providing IFU as a separate document to the PI within the package leaflet.

The sponsor is required to comply with product vigilance and risk minimisation requirements.

The TGA may request an updated RMP at any stage of a product's life cycle, during both the pre-approval and post-approval phases. Further information regarding the TGA's risk management approach can be found in risk management plans for medicines and biologicals and the TGA's risk management approach. Information on the Australia-specific annex (ASA) can be found on the TGA website.

Risk-benefit analysis

Delegate's considerations

As the sponsor is aware, all injectable products not administered by a healthcare professional must include the PI with the product as a package insert. The ASA has been updated to state that Eladynos will be supplied with the PI as a package insert and the sponsor has updated the PI to include instructions for use (IFU). To improve readability of PI, the sponsor should consider providing IFU as a separate document to the PI. This issue should be addressed prior to finalisation of the PI. Final acceptability of the PI will be determined at PI approval phase.

Proposed action

The sponsor's response is satisfactory and no further PI changes are requested from an RMP perspective. The final acceptability of the PI will be determined during the PI approval phase.

Outcome

Based on a review of quality, safety, and efficacy, the TGA decided to register Eladynos (abaloparatide) for the following indication:

> *"Eladynos is indicated for the treatment of osteoporosis in postmenopausal women at increased risk of fracture."*

Specific conditions of registration applying to these goods

Black Triangle Scheme

Eladynos (abaloparatide) is to be included in the Black Triangle Scheme. The PI and CMI for Eladynos must include the black triangle symbol and mandatory accompanying text for five years, which starts from the date that the sponsor notifies the TGA of supply of the product.

RMP Conditions

The Eladynos EU-Risk Management Plan (RMP) (version 0.5, dated 11 October 2022, data lock point 27 April 2022), with Australian Specific Annex (version 1.1, dated 27 June 2024), included with submission PM-2023-05942-1-5, and any subsequent revisions, as agreed with the TGA will be implemented in Australia.

An obligatory component of risk management plans is routine pharmacovigilance. Routine pharmacovigilance includes the submission of periodic safety update reports (PSURs).

PSUR conditions

Reports are to be provided in line with the current published list of EU reference dates and frequency of submission of PSURs until the period covered by such reports is not less than three years from the date of this approval letter. Each report must be submitted within ninety calendar days of the data lock point for that report.

The reports are to at least meet the requirements for PSURs as described in the European Medicines Agency's Guideline on good pharmacovigilance practices (GVP) Module VII periodic safety update report (Rev 1), Part VII.B Structures and processes. Note that submission of a PSUR does not constitute an application to vary the registration.

Attachment 1. Product Information

The Product Information (PI) approved with this submission for Eladynos which is described in this AusPAR, can be found as Attachment 1. 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 #