Abaloparatide for treating osteoporosis in postmenopausal women

For screen – contains no confidential data

Technology appraisal committee A [14 May 2024]

Chair: Radha Todd

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Company: Theramex

Abaloparatide for treating osteoporosis

- ✓ **Background and key issues**
- ❑ Clinical effectiveness
- ❑ Modelling and cost effectiveness
- ❑ Other considerations
- ❑ Summary

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Background on osteoporosis

Progressive skeletal disorder characterised by reduced bone density

Symptoms

- Loss of height over time, stooped posture, fracture of vertebrae, hip or other bones. Often undiagnosed until fracture occurs.

Diagnosis and classification

- a bone mineral density 2.5 standard deviations below the mean value for a young healthy adult (i.e., a T-score of ≤ -2.5), as measured by dual energy X-ray absorptiometry at the femoral neck
- UK clinical guidelines suggest treatment based on risk rather than solely bone density readings

Epidemiology

- In England and Wales, more than 2 million women have osteoporosis
- Prevalence of osteoporosis increases with age; ~2% at 50yrs to ~50% at 80yrs
- The lifetime risk of fragility fracture for a 50yr old women is 35% (inc. 17.2% lifetime risk of hip fracture)[1]

Causes

- Risk factors include hormonal changes (e.g. after menopause), certain medications, family history, and lifestyle factors (e.g. low intake of calcium/vitamin D, lack of exercise, heavy drinking/smoking)

1. Borgstrom F et al (2020)

Clinical & Patient perspectives

Patients and clinicians welcome an additional treatment option

Patient perspective from Royal Osteoporosis Society and patient experts:

- Osteoporosis affects mental health; people can become anxious and withdrawn
- Care is patchy across UK, and many suffer avoidable secondary fractures
- Current options for anabolic treatment limited, with strict criteria for use
- Existing drugs linked with rare but serious side effects (osteonecrosis of the jaw and atypical fractures), which limits uptake/concordance
- Abaloparatide not associated with these risks - important advantage for patients
- Injections (vs tablets) and having to wait to see a specialist may be seen as disadvantage

"I am constantly afraid of falling, as are most people with osteoporosis"

Patient expert

Clinical perspective from British Society for Rheumatology and clinical expert:

- Addresses unmet need in those unable to have romosozumab or teriparatide (due to side effects/eligibility)
- Would be used as a first line option in patients at particularly high risk, or alternate second line option
- Totality of evidence (inc. RWE) suggests anti-fracture efficacy of abaloparatide equal or greater than teriparatide
- Use will be similar to existing technologies; no significant practical implications
- Investment in DEXA scans needed if eligibility based on T scores
- UK clinical guidelines (CG146) suggest treatment based on risk rather than bone density readings
- Eligibility based on BMD risks excluding those unable to have DEXA scan (mobility issues, local availability)

BMD = bone mineral density; RWE = real world evidence;

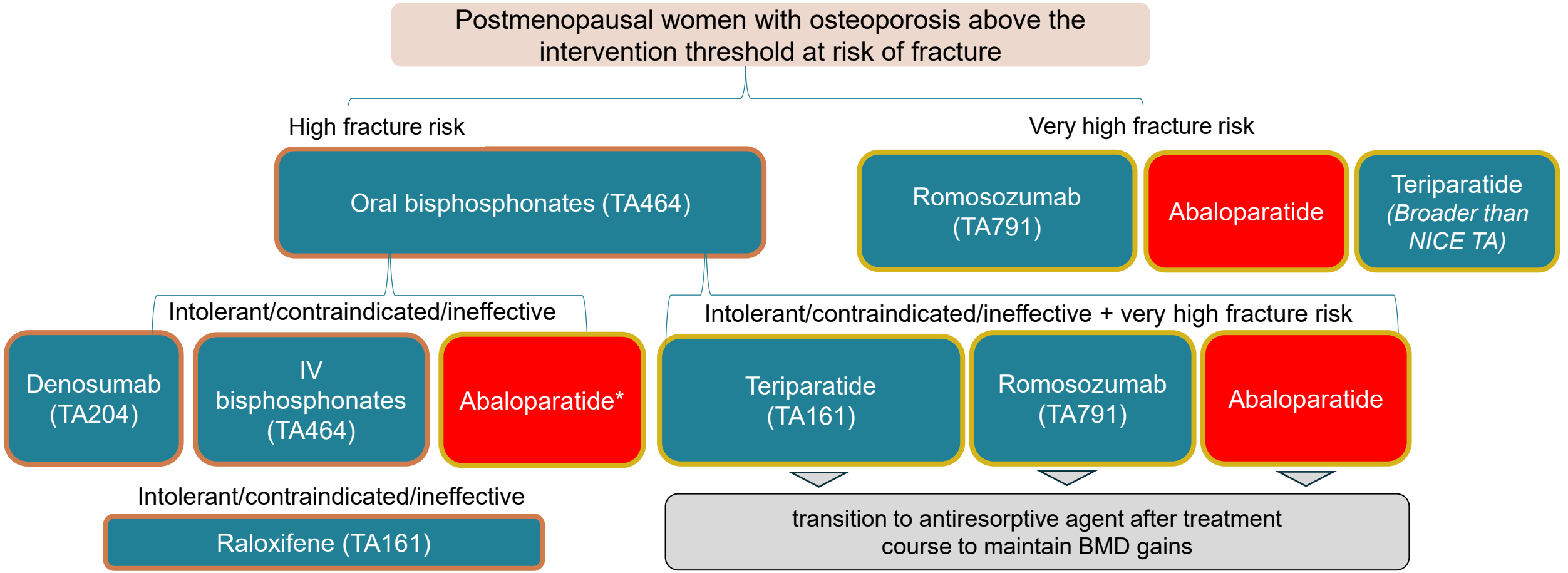
Equality considerations

Issue raised by company:

- Abaloparatide MA is for ‘postmenopausal women’
- People who have been through menopause but do not identify as a woman should also be able to use abaloparatide. TA791 for romosozumab did not specify sex in recommendations.

Simplified treatment pathway

Antiresorptive agents (slows bone breakdown)
Anabolic agents (stimulates bone formation)



NOTE: there are differences in definitions (e.g. high/severe/imminent risk) and intervention thresholds used across TAs, clinical guidelines, clinical trials and marketing authorisations. This makes the pathway more complex than the simplified version above.

* No previous fracture but higher-risk due to other factors (age/BMD)

Abaloparatide (Eladynos, Theramex)

Marketing authorisation	Marketing authorisation granted March 2023: • Treatment of osteoporosis in postmenopausal women at increased risk of fracture
Mechanism of action	• Anabolic agent (stimulates bone formation) • Synthetic analogue of parathyroid hormone-related protein (PTHrP), a molecule naturally involved in bone growth and development.
Administration	• Subcutaneous injection, once a day • Refrigeration not required (unlike teriparatide)

Price	• List price:
	  • £294.54 for one-prefilled pen with 30 doses in 1.5 mL solution
	  • £5,301.72 for a fixed-duration 18-month treatment
	• Commercial arrangement in place (simple PAS discount)

Positioning is narrower than marketing authorisation – only includes people at 'very high risk of fracture'

Recap of the appraisal

- Original company submission was received Sept 23
- EAG identified numerous concerns in the economic model and did not consider it fit for purpose
- Some of these concerns were addressed during the clarification stage, but others were still outstanding, so a second clarification stage was added (CQ2)
- In CQ2 the company submitted an updated network meta-analysis and cost effectiveness model
- It was this updated model and analyses which informed the EAG report
- There was no technical engagement stage for this topic
- During the company's factual accuracy check of the EAG report, the company indicated that new data and analyses were available to support its submission. However, this was too late in the process for the EAG to review and critique this data in time for this committee meeting. So the additional information has not been accepted (or received) at this stage.

Key issues

Issue	Slide
Generalisability of trial data to current practice	Link to slide
Model issues & errors	See EAG report
Estimation of uncertainty in relative treatment effects	Link to slide
Treatment effect for abaloparatide vs. teriparatide	Link to slide
Assumptions and sources for persistence rates	Link to slide
Application of long-term care costs	Link to slide
Utilities not applied for nursing home admission	Link to slide
Resource use for disease management	Link to slide

Impact of each issue on ICER varies according to comparator and other preferred assumptions

Abaloparatide for treating osteoporosis

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- ❑ Other considerations
- ❑ Summary

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ACTIVE trial results – vertebral & nonvertebral fractures

Abaloparatide reduces risk of new vertebral fractures vs placebo

	Study participants with fracture, n (%)			Abaloparatide vs placebo		Abaloparatide vs teriparatide	
	Abal. (n=696)	Placebo (n=688)	Teri. (n=686)	ARR (%) (95% CI)	HR, *unless stated* (95% CI)	ARR (%) (95% CI)	HR (95% CI)
New vertebral fracture (Primary endpoint, mITT)	(n=583) 3 (0.5)	(n=600) 25 (4.2)	(n=600) 4 (0.7)	**–3.65 (–5.59 to –2.00)**	**RRR, –0.88 (–0.96 to –0.59)**	Not reported due to insufficient power	
				p-value <0.001			
Nonvertebral fracture¶ Secondary endpoint (ITT population)	15 (2.7)	21 (3.6)	12 (2.0)	–0.87 (–2.89 to 1.15)	0.74 (0.38 to 1.43)	–0.73 (–1.01 to 2.48)	1.30 (0.61 to 2.79)
				p-value = 0.368		p-value = 0.49	

- Abaloparatide reduced the risk of new vertebral fractures by 88% vs placebo at 18 months (p<0.001)
- For nonvertebral fractures, the results were not significant for abaloparatide vs placebo or teriparatide

Supplementary appendix includes overview of key trials, trial design, and baseline characteristics

¶ Nonvertebral fractures = fractures not occurring in the spine or skull, such as the hip, wrist, and forearm

BOLD = statistically significant result; ARR = absolute risk reduction; CI = confidence interval; HR = hazard ratio; RRR = relative risk reduction;

ACTIVE trial results – major osteoporotic & clinical fractures

Abaloparatide reduces major osteoporotic fracture risk vs placebo

	Study participants with fracture, n (%)			Abaloparatide vs placebo		Abaloparatide vs teriparatide	
	Abal. (n=696)	Placebo (n=688)	Teri. (n=686)	ARR (%) (95% CI)	HR (95% CI)	ARR (%) (95% CI)	HR (95% CI)
Major osteoporotic fracture[Ŧ]	7 (1.2)	23 (5.4)	14 (2.2)	**–4.48 (–7.80 to –0.56)**	**0.31 (0.13 to 0.72)**	–1.04 (–2.50 to 0.42)	0.51 (0.21 to 1.27)
				P value = 0.004		P value = 0.14	
Clinical fracture[¶]	21 (3.8)	35 (7.4)	21 (3.4)	–3.64 (–7.63 to 0.35)	0.61 (0.36 to 1.06)	0.33 (–1.82 to 2.47)	1.04 (0.57 to 1.90)
				P value = 0.08		P value = 0.90	

- Abaloparatide group had 69% lower risk of major osteoporotic fracture vs. the placebo group at 19 months (HR = 0.31, p=0.004)
- Non-significant results for abaloparatide vs teriparatide, and for abaloparatide vs placebo in clinical fracture

Supplementary appendix contains data from Real Word Evidence study

[Ŧ] Major osteoporotic fracture = upper arm, wrist, hip, or clinical spine
[¶] Clinical fracture = all fractures that would cause a patient to seek medical care, regardless of the level of trauma, including spine pain
BOLD = statistically significant result; ARR = absolute risk reduction; CI = confidence interval; HR = hazard ratio;

ACTIVExtend trial results

Longer-term data consistent with ACTIVE study results

- EAG: efficacy findings for ACTIVExtend were 'entirely consistent with the findings for the ACTIVE trial' for all key outcomes (at 43-months).
- Risk of ≥1 new vertebral fracture reduced by 84% in intervention group vs placebo

	Endpoint	ACTIVExtend	
		Placebo/alendronate	Abaloparatide/ alendronate
Primary end point (mITT population)		**n=489**	**n=457**
≥1 new vertebral fracture, n (%)	ARR (%) (95% CI)	**–4.44 (–6.86, –2.30)**	
	RRR (95% CI; p value)	**–0.84 (–0.94, –0.53; p<0.001)**	
Secondary endpoints (ITT population): KM estimates		**n=494**	**n=469**
≥1 nonvertebral fracture	ARR (%) (95% CI)	–2.53 (–5.42, 0.36)	
	HR (95% CI; p value)	0.61 (0.35–1.08; p=0.088)	
≥1 major osteoporotic fracture, n (%)	ARR (%) (95% CI)	**–2.98 (–5.57, –0.38)**	
	HR (95% CI; p value)	**0.48 (0.25–0.92; p=0.024)**	
≥1 clinical fracture	ARR (%) (95% CI)	–2.61 (–5.97, 0.74)	
	HR (95% CI; p value)	0.68 (0.42–1.10; p=0.119)	

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BOLD = statistically significant result
ARR = absolute risk reduction; CI = confidence interval; HR = hazard ratio; RRR = relative risk reduction

Network meta-analysis

NMA conducted due to lack of head to head data with some comparators

These data inform the company base case:

	HR vs placebo (95% CrI)		
	New vertebral fracture (S=20)	Hip (S=17)	Non-vertebral fracture (S=18)
Abaloparatide	[redacted]	[redacted]	[redacted]
Romosozumab	[redacted]	[redacted]	[redacted]
Teriparatide	[redacted]	[redacted]	[redacted]
Alendronate	[redacted]	[redacted]	[redacted]

For new vertebral fractures, abaloparatide had greatest reduction vs placebo

Company: 'findings from the NMA suggest abaloparatide has comparable efficacy to other non-bisphosphonates (teriparatide, romosozumab and denosumab) and bisphosphonates for reducing fractures'

Abaloparatide vs Teriparatide; NMA compared to ACTIVE and RWE

	New vertebral fracture		Hip				Non-vertebral fracture		
HR, unless stated (95% CrI/CI)	ACTIVE	NMA	ACTIVE	RWE study	RWE (>12m cons. treatment)	NMA	ACTIVE	RWE study	NMA
	RRR*~ -0.23 [Equiv RR ~ 0.77]	[redacted]	n/e	0.78 (0.62,1.00)	0.57 (0.35,0.94)	[redacted]	1.30 (0.61 - 2.79)	0.89 (0.77,1.03)	[redacted]

*Not estimated in CS; CI = confidence interval; CrI = credible interval; HR = hazard ratio; n/e = not estimated; NMA = network meta analysis; RR = relative risk RRR = relative risk reduction

Key issues: Generalisability of ACTIVE to current practice

EAG says trial population isn't aligned with use of anabolic therapy in NHS

Background

- ACTIVE trial included some people with no previous fracture (if aged 65+ and T-score ≤ -3.0)

EAG comments

- >40% of the patients in ACTIVE would not be eligible for either teriparatide or romosozumab on NHS (as no previous fracture)
- Also, some people wouldn't be considered at 'very high risk' of fracture according to the NOGG guideline
- Trial excluded people with prior bisphosphonate treatment, but company's positioning includes both with and without prior bisphosphonate treatment
- EAG has conducted a scenario analysis using characteristics of patients with a prior fracture at baseline*

Company

- Aiming to do targeted post-hoc analyses to demonstrate safety & efficacy across population subgroups

Is current data suitable for decision making or is further analysis needed?

* Population from ARCH study (trial of romosozumab)
NOGG = National Osteoporosis Guideline Group;

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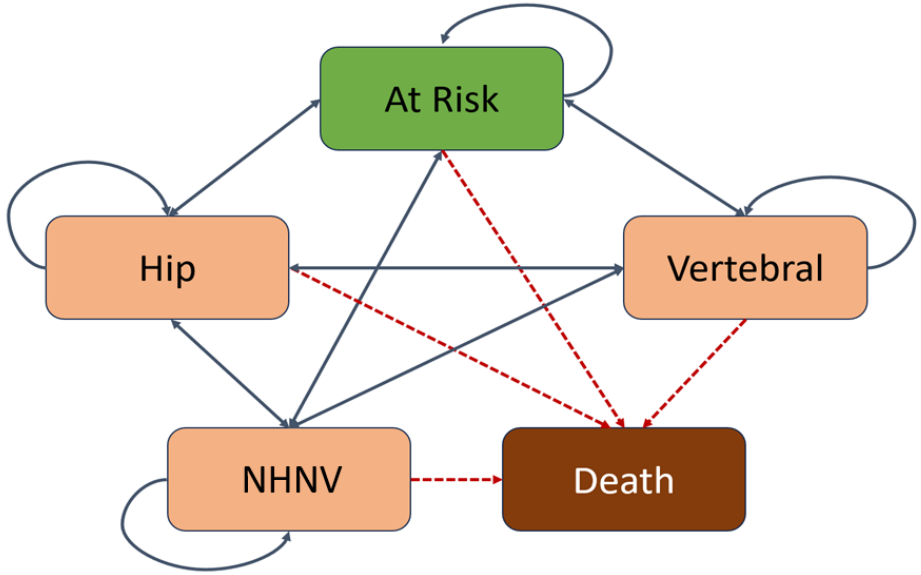
Model structure and health states

State-transition patient-level microsimulation model:



Population	**Postmenopausal women with osteoporosis at very high risk of fracture**
Time horizon	Lifetime (maximum of 50 years)
Intervention	Abaloparatide
Comparator	• Teriparatide • Romosozumab
Perspective	NHS and PSS
Discount rate	3.5% for health outcomes and costs

- Patients who have had a fracture return to the 'at risk' state after 1 cycle (unless they incur a new fracture or die)
- Probability of fracture in the model based on;
  - general population risk
  - increased risk from baseline patient characteristics (FRAX)
  - increased risk of subsequent fracture after an incident fracture
- Fractures per patient limited to 2 hip, 4 vertebral and 10 NHNV (in line with TA464 and Davis et al. (2020)

FRAX = Fracture Risk Assessment Tool; NHNV = Non-hip-nonvertebral fractures;

Key Issue: Estimation of uncertainty in relative treatment effects

EAG says uncertainty may be underestimated in company's PSA

Background

- Company and EAG have different approaches to capture the uncertainty around the HRs used in the PSA

Company

- To capture uncertainty around treatment effect, HRs were sampled for each treatment independently from a gamma distribution (standard error =5% of the mean HR).
- Probabilistic results are consistent with the deterministic analysis

EAG comments

- Uncertainty in the cost-effectiveness estimates may be substantially underestimated in company's PSA
- In company PSA abaloparatide has better efficacy (vs. romo & teri) for hip fracture in >95% of the PSA runs - doesn't align with NMA results where 65% of CODA samples provide better efficacy for abaloparatide
- Company approach provides narrower CIs and does not capture any correlations between the HRs
- EAG prefers to use the CODA samples from the NMA to reflect the uncertainty around the HRs in PSA
- EAG approach maintains the correlation between the HRs from the NMA and also ensures that the same set of sampled HRs are applied to every patient in the cohort
- Preferred approach impacts average costs and QALYs

What is committee's preferred approach to capture the uncertainty around treatment effect estimates?

CODA = convergence diagnosis and output analysis; HR = hazard ratio; NMA = network meta-analysis; PSA = probabilistic sensitivity analysis; QALY = quality adjusted life-year;

Key issue: Treatment effect for abaloparatide vs. teriparatide

EAG prefers to assume abaloparatide has same efficacy as teriparatide for hip & NHNV outcomes

Background

- Company has used NMA outputs to capture the expected HRs for each treatment versus placebo

Company

- Latest RWE for abaloparatide gives additional insights into treatment effect, particularly hip and NHNV fracture outcomes when compared to teriparatide (*data hasn't been provided as insufficient time for review*)

EAG comments

- NMA is uncertain and based on very few events - prefer to assume abaloparatide has same efficacy as teriparatide for both hip and NHNV outcomes
- For hip fracture, HR based on 1 event in placebo arm and 0 in abaloparatide arm (ACTIVE study)
- For NHNV fractures, HRs for abaloparatide versus teriparatide were inconsistent with the findings of the RWE study (opposite direction of treatment effect for the median HR)
- Important impact on the cost-effectiveness estimates

HRs used in company/EAG base cases and cost comparison scenario can be found here.

Does committee prefer to use NMA outputs or assume equal efficacy for abaloparatide vs teriparatide (hip & NHNV outcomes)

HR = hazard ratio; NHNV = Non-hip-nonvertebral fractures; NMA = network meta-analysis; RWE = real world evidence;

Key issue: Assumptions and sources for persistence rates

EAG says treatment persistence for romosozumab should have linear decline

Background

- Company has assumed 80% treatment persistence for romosozumab at both 6m and 12m.

Company

- Persistence rates for romosozumab were taken from the conservative estimate used in the economic evaluation of romosozumab reported in Söreskog et al. (2021)
- This was preferred choice of EAG for romosozumab NICE appraisal (TA791)
- Persistence rates for teriparatide and abaloparatide taken from UK RWE study

EAG comments

- Linear decline in treatment persistence has been assumed for abaloparatide and teriparatide – should be same approach for romosozumab
- EAG assumes linear decline for romosozumab from 0-12 months (90% at 6 months, 80% at 12 months)
- Company scenario analyses uses ACTIVE trial data for abaloparatide and teriparatide but still applies 80% fixed rate for romosozumab (rather than romosozumab trial data)
- EAG scenario analysis applies trial-based estimates for all treatments (inc ARCH data for romosozumab).

Does committee prefer company base case approach, EAG linear decline or EAG trial based estimates?

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RWE = real world evidence;

Key issue: Application of long-term care costs

EAG prefers patient-level approach for long-term care costs (vs. cohort-level)

Background

- Company model uses a patient-level state transition structure to simulate fractures occurring, but a cohort-level approach for costs related to long-term care admissions

Company

- Proportion of long-term care costs are allocated to every individual having a hip fracture, rather than simulating whether the individual is admitted to long-term care.

EAG comments

- Prefer individual-level approach, where admission to long-term care is simulated for each individual experiencing a hip fracture
- This is aligned with the approach for simulating fracture and estimating costs and utilities, which are applied according to the individual's specific fracture history

Should long term care costs be applied via patient-level or cohort-level approach?

Key issue: Utilities not applied for nursing home admission

EAG says HRQoL impact of care home admission is underestimated

Background

- Company model has no loss in HRQoL for patients whose hip fracture results in a new admission to long-term care vs. those who return to living in their own home
- A survey quoted by the company found that 80% of older women would rather be dead than experience the loss of independence and QoL resulting from a hip fracture and subsequent admission to nursing home

Company

- Utilities data comes from ICUROS study; largest and most recent prospective study that collected EQ-5D
- ICUROS study was also the accepted source of utility values in TA791

EAG comments

- Utility multiplier can be applied for long-term care, but may result in some double counting of utility decrement (so not included in EAG base case)
- EAG scenario analysis uses multiplier of 0.625 – taken from TA464 (bisphosphonates for osteoporosis)
- Small impact on the cost-effectiveness estimates in the EAG's preferred base case but potential for larger impact if the NMA HRs are used

Should utility decrement be applied for admission to a nursing home? If so, is 0.625 multiplier appropriate?

HR = hazard ratio; HRQoL = health-related quality of life; NMA = network meta analysis; QoL = quality of life;

Key issue: Resource use for disease management

EAG uses different estimates of resource use and unit costs for disease management

Background

- Company base case includes 2 GP practice nurse visits per year, and a diagnostic imaging procedure BMD measurement every 2 years.

Company

- Resource use assumptions were based on NICE TA791 and Hiligsmann et al.

EAG comments

- Company's model did not reflect EAG clinical expert advice
- Cost of GP letter and initial specialist consultation not included in model costs, other costs underestimated
- EAG prefers to include/increase costs relating to DEXA scans (one at start & end of treatment), nurse visits (1 at start of treatment) and specialist consultations (every 6m on romosozumab and abaloparatide)
- EAG also prefers some different unit costs to company (e.g. £95 vs. £40 for BMD measurement)

Health state resource use and costs used in company/EAG base cases can be found here.

Does committee prefer company or EAG resource use and unit cost assumptions?

BMD = bone mineral density;

Summary of company and EAG base case assumptions

Assumption	Company base case	EAG base case
Efficacy		
Hip fractures	HRs from NMA	Assume same efficacy for abaloparatide vs teriparatide (as HRs from NMA are too uncertain)
Non-hip non-vertebral fractures	HRs from NMA	Assume same efficacy for abaloparatide vs teriparatide (as HRs from NMA are inconsistent with RWE)
Uncertainty around HRs	Sampled HRs for each treatment independently from gamma distribution	Used CODA samples
Treatment persistence	80% treatment persistence for romosozumab at both 6m and 12m	Linear decline in treatment persistence for romosozumab over 12 months
Long-term care costs	Cohort-level approximation for long-term care cost	Individual patient-level approximation for long-term care cost
Resource use	• DEXA scan every 2 years • 1 specialist consultation for all patients at start of treatment • No further nurse visits following treatment administration	Different resource use and unit cost assumptions: • 1 DEXA scan at treatment start, 1 at end • Specialist consultation every 6 months for romosozumab & abaloparatide, 1 each year for teriparatide • 1 nurse visit over the course of treatment

CODA = convergence diagnosis and output analysis; HR = hazard ratio; NMA = network meta analysis; RWE = real world evidence;

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Key questions for Committee

- Is ACTIVE data suitable for decision making or is further analysis needed?
- What is committee's preferred approach to capture the uncertainty around treatment effect estimates?
- Does committee prefer to use NMA outputs or assume equal efficacy for abaloparatide vs teriparatide (hip & NHNV outcomes)
- Does committee prefer company base case approach, EAG linear decline or EAG trial based estimates for romosozumab persistence rates?
- Should long term care costs be applied via patient-level or cohort-level approach?
- Should utility decrement be applied for admission to a nursing home? If so, is 0.625 appropriate?
- Does committee prefer company or EAG resource use and unit cost assumptions?

NHNV = Non-hip-nonvertebral fractures; NMA = network meta analysis;

Impact on cost effectiveness

Due to confidential discounts, all ICERs will be presented in Part 2 of the meeting

Issue	Slide	Impact on modelling
Generalisability of trial data to current practice	Generalisability	• All key issues have a very small impact on incremental QALYs vs company base case (<0.05 QALYs) • Due to QALYs being very similar between treatments, small differences in costs can have a large impact on ICERs • The treatment effect for abaloparatide vs. teriparatide is the issue which has the largest impact on cost effectiveness • Abaloparatide is cost effective in some, but not all comparisons/scenarios
Model issues & errors	n/a	
Estimation of uncertainty in relative treatment effects	Estimation of uncertainty	
Treatment effect for abaloparatide vs. teriparatide	Treatment effect	
Assumptions and sources for persistence rates	Persistence rates	
Application of long-term care costs	Long-term care costs	
Utilities not applied for nursing home admission	Nursing home costs	
Resource use for disease management	Resource use	

ICER = incremental cost-effectiveness ratio; QALY = quality adjusted life-year;

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Thank you.

Supplementary appendix

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Decision problem

	Final scope	Company	EAG comments
Population	Postmenopausal women with osteoporosis at increased risk of fracture	Postmenopausal women with osteoporosis at very high risk of fracture	'Very high risk" in ACTIVE trial doesn't match NOGG guideline definition.
Intervention	Abaloparatide	Abaloparatide for 18 months, followed by alendronate	Other subsequent treatments could be used rather than alendronate
Comparators	• Bisphosphonates (alendronic acid, ibandronic acid, risedronate sodium, zoledronic acid) • Non-bisphosphonates (denosumab, romosozumab, strontium ranelate, teriparatide, raloxifene) • No active treatment	• Teriparatide for 24 months followed by alendronate • Romosozumab for 12 months followed by alendronate Abaloparatide would be used before bisphosphates, rather than instead of them	IV zoledronate would also be a relevant comparator for some patients (no previous fracture but higher risk due to age + BMD).

Decision problem

	Final scope	Company	EAG comments
Outcomes	• Osteoporotic fragility fracture • Bone mineral density • Mortality • Adverse effects of treatment • Health-related quality of life	In line with scope	Overall, EAG is satisfied the CS covers the outcomes specified in the scope where available.
Subgroups	• predicted risk of fracture over 10 years • patient characteristics that affect the impact of fracture on lifetime costs and outcomes • fracture history		economic analysis for the subgroup with a prior major osteoporotic fracture in the previous 24 months would be useful as this is the population specified for romosozumab

CS = company submission;

Key clinical trials

	ACTIVE (N=2,070)	ACTIVExtend (N=963)	RWE (N=23,232)
Design	Phase 3, randomised, placebo- and active-controlled, partially open-label trial	Open-label extension study	retrospective observational study (USA)
Population	Postmenopausal women with osteoporosis at very high risk of fracture		Women ≥50yrs on abaloparatide or teriparatide and no prior anabolic therapy
Intervention	Abaloparatide	Abaloparatide then alendronate	Abaloparatide or teriparatide
Comparator(s)	Placebo or teriparatide	Placebo followed by alendronate	N/A
Duration	18 months	24-month extension study	19 months
Primary outcome	% with 1+ new vertebral fracture	% with 1+ new vertebral fracture	time to first nonvertebral fracture event
Key secondary outcomes	• nonvertebral fractures at 18m • % change in BMD	• incidence and time to first event • % change in BMD • changes in serum markers	• CV safety
Used in model?			

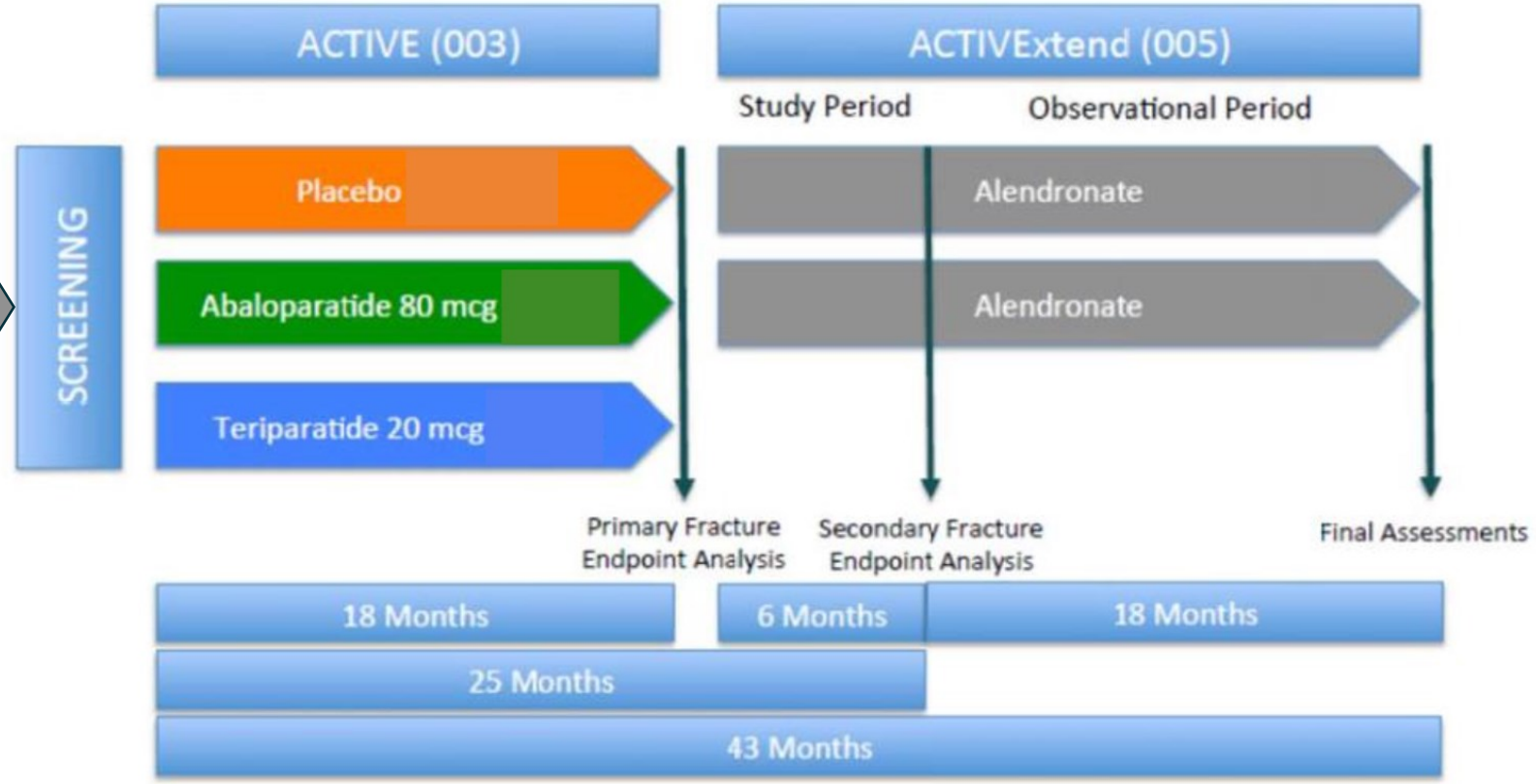
No UK centres in ACTIVE/ACTIVExtend

BMD = bone mineral density; CV = cardiovascular

ACTIVE & ACTIVExtend trial design

Healthy postmenopausal women aged 49–86 with:

- Current/previous fracture and
  - T-score ≤-2.5 and >-5.0
  - Or, T-score ≤-2.0 and >-5.0 and 65yrs+
- T-score ≤ -3.0 and > -5.0 aged 65yrs+



- EAG judges ACTIVE trial to be at high risk of bias overall*. This is due to high attrition rate (resulting in missing data) and some concerns over randomisation process and selection of reported results
- Demographic and baseline characteristics were generally well-balanced among treatment groups

*Using the Cochrane Risk of Bias tool

ACTIVE - Baseline characteristics

EAG says baseline characteristics 'generally well-balanced'

	Placebo n=688	Abaloparatide n=696	Teriparatide n=686
Age, mean (SD), years	69.3 (6.1)	69.5 (6.3)	69.4 (6.1)
Weight, mean (SD), (kg)	60.3 (9.8)	60.0 (9.7)	60.2 (10.2)
BMI, mean (SD), (kg/m^2)	24.9 (3.5)	24.8 (3.5)	25.0 (3.5)
T-score, mean (SD):			
Femoral neck	–2.2 (0.7)	–2.2 (0.6)	–2.2 (0.7)
Total hip	–1.9 (0.8)	–1.9 (0.7)	–1.9 (0.8)
Lumbar spine	–3.0 (0.8)	–2.9 (0.9)	–2.9 (0.9)
Severe disease, n (%)[b]	127 (18.5)	113 (16.3)	142 (20.7)
No history of prior fracture, n (%)	297 (43.2)	289 (41.5)	289 (42.1)

EAG: Baseline characteristics were generally well-balanced among treatment groups.

NICE

BMI = body mass index; SD = standard deviation;

Results from Real World Evidence study

RWE shows noninferiority of abaloparatide vs teriparatide for primary endpoint

- A 19-month RWE retrospective observational study from the US provides additional data on abaloparatide and teriparatide in postmenopausal women with osteoporosis (n=23,232)
- Study results showed:
  - Noninferiority of abaloparatide vs teriparatide for time to first nonvertebral fracture (primary endpoint)
  - risk of hip fractures (exploratory endpoint) reduced by 22% (0–33%) for abaloparatide vs teriparatide

Time to event variable	Parameter	Abaloparatide (n=11,616)	Teriparatide (n=11,616)
Non-vertebral fracture	Number of patients with event, n (%)	335 (2.9)	375 (3.2)
	HR (95% CI) vs teriparatide	0.89 (0.77–1.03)	
	p-value vs teriparatide	0.13	
Hip fracture	Number of patients with event, n (%)	121 (1.0)	154 (1.3)
	HR (95% CI) vs teriparatide	0.78 (0.62–1.00)	
	p value vs teriparatide	0.04	

NICE

HR = hazard ratio; RWE = real world evidence;

Clinical inputs used in company cost-effectiveness model

	Parameter	Source
Patient characteristics	Age	Abaloparatide arm in ACTIVE (mITT population). T-score annual variation based on Stevenson et al. (2007).[54]
	FRAX characteristics at baseline	
Mortality	General population mortality	UK life tables (Age- and sex-matched)
	Excess mortality related to fractures	Staa et al. (2007)
Risk of fractures	Risk of fractures in general population	Singer et al. (1998), Kanis et al. (2000)[57] and NICE previous appraisal for romosozumab (TA791)[43]
	Fracture risk for modelled population	FRAX algorithm
	Risk of imminent fractures after incident fracture	Söreskog et al. (2020)
	Risk reduction due to treatment effect	Company NMA.
Treatment persistence	ACTIVE study, Söreskog et al. (2021a and 2021b) and Morley et al. (2020).	
HRQoL	General population and 'at risk' state utilities	Hernández Alava et al. (2022).
	Utility multipliers for fracture states (hip, vertebral and 'other')	ICUROS study* (similar approach to TA791)
	QALY losses related to AEs	Not included.

Hazard ratios used in cost-effectiveness models

Relative risks for each treatment used in the company's base-case, EAG base case and the EAG's cost comparison scenario:

Analysis type	Company base case			EAG base case			EAG cost comparison scenario		
Fracture type	Abalop.	Terip.	Romos.	Abalop.	Terip.	Romos.	Abalop.	Terip.	Romos.
Hip	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]		[redacted]	
Vertebral	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]		[redacted]	
NHNV	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]		[redacted]	

Abalop. = abaloparatide; NHNV = non-hip non-vertebral; Romos. = romosozumab; Terip.= teriparatide.

Health state resource use and costs

One-off cost and per 6-month cycle

		Company base case		EAG base case			
		Initial treatment	Subsequent treatment	Initial treatment	Initial treatment	Initial treatment	Subsequent treatment
		Abalo/romo/teripa	Alendronate	Abaloparatide	Romosozumab	Teriparatide	Alendronate
Drug admin cost (one-off, at treatment initiation)		£12	£0	£16	£16	£16	£16
Disease management (one-off, at treatment initiation)	Nurse visits	£0	£0	£135	£135	£135	£0
	BMD measurement	£0	£0	£95	£95	£95	£0
	Specialist consultation	£0	£0	£221	£221	£221	£0
	Reporting to referrer	£0	£0	£1	£1	£1	£0
Total one-off-cost		**£12**	**£0**	**£468**	**£468**	**£468**	**£0**
Disease management (on-going per cycle costs)	Nurse visits	£7	£7	£0	£0	£0	£0
	BMD measurement	£10	£10	£32	£48	£24	£0
	Specialist consultation	£0	£0	£221	£221	£110	£22
Total ongoing cost (per cycle)		**£17**	**£17**	**£253**	**£268**	**£134**	**£22**

Taken from Table 53 of EAR

BMD = bone mineral density;