NICE National Institute for Health and Care Excellence

Romosozumab for treating severe osteoporosis [ID3936]

Lead team presentation

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4th November 2021

Key issues

Issue	ICER impact
Patient population: which is appropriate for decision making?	
Comparators: which are most relevant?	
Duration of treatment effect: should this be limited (e.g., to 42 months after starting treatment)?	
Network meta-analyses: appropriate for decision making?	
Persistence: which rates should be used in the model?	
Fracture utility multipliers: robust for decision making?	
Excess mortality: which fracture types should this be attributed to?	
Fracture costs: should absolute or incremental fracture costs be used?	
Daily long-term care / administration costs: which should be used in the model?	 / 
Cardiovascular adverse events: should these be included in the model?	

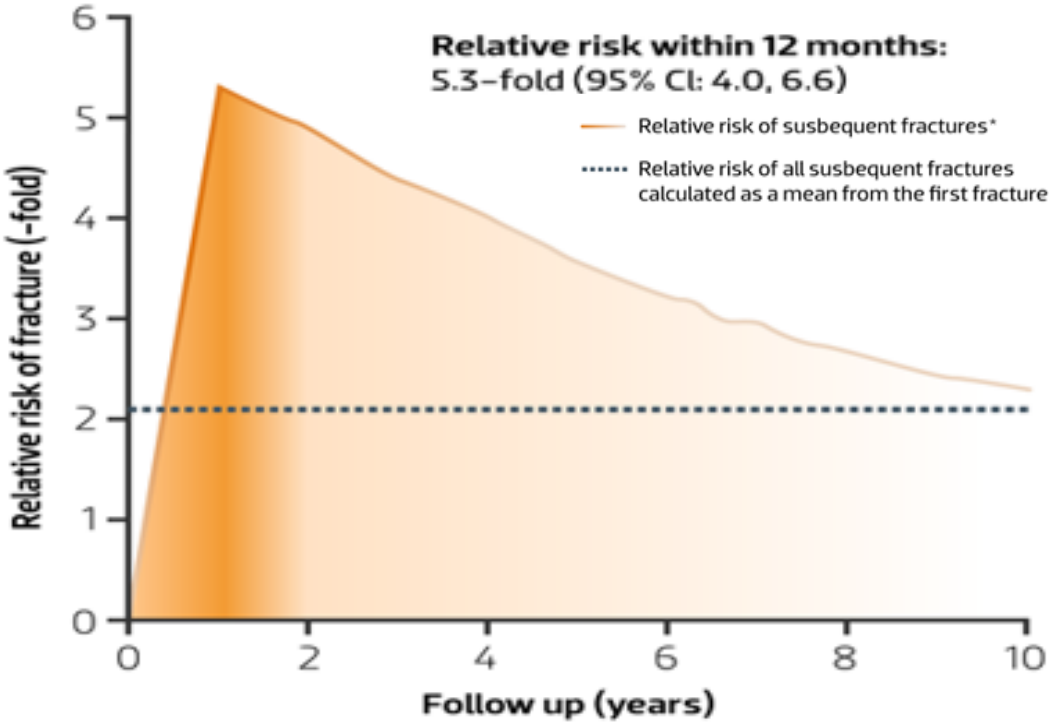
Key: Large impact  Small/moderate impact  Unknown impact 

Background: osteoporosis

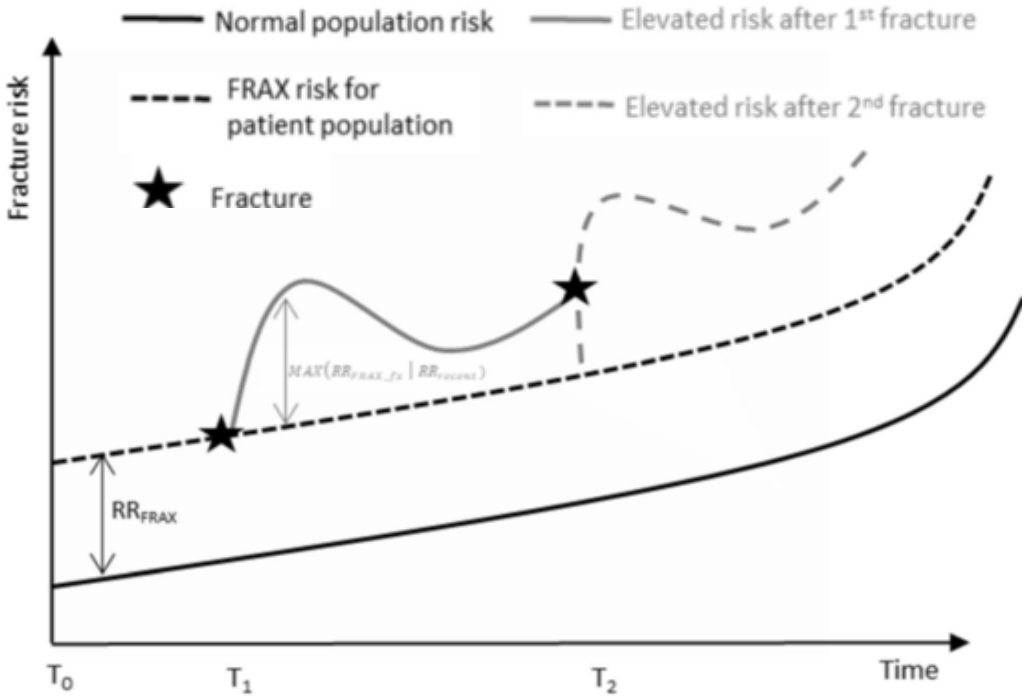
- **Osteoporosis:** progressive skeletal disorder, characterised by low bone mass, deterioration of bone tissue structure, increase in bone fragility and risk of fracture. Asymptomatic and often undiagnosed until fracture
- **Fragility fractures:** result in considerable disability and pain, and lead to significant impairments in mobility. Can have a long-lasting impact for a patient's health-related quality of life and are associated with significantly increased mortality
- **Symptoms of osteoporosis:** include back pain, loss of height over time, stooped posture, fracture of vertebrae, hip or other bones
- **Diagnosis:** 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
- **Epidemiology:** around 3.5 million people over the age of 50 years in the UK are living with osteoporosis. One third of postmenopausal women suffer a fragility fracture due to osteoporosis in their lifetime, and there are an estimated 536,000 fragility fractures in the UK each year
- **Treatments:** generally fall into 2 classes, bone-forming/anabolic agents (teriparatide) and anti-resorptive agents (bisphosphonates, denosumab and raloxifene). Romosozumab considered both bone forming and anti-resorptive

Imminent risk of fracture in osteoporosis

A fracture is a major risk factor for future fractures



Relative risk of subsequent fractures



Risk trajectory used in economic model

Company

- Relative risk of fracture sharply increases and is highest in the two years after a fracture, during this time people are at imminent risk of another fracture
- Considered population who experienced a fracture based on marked elevation in risk observed in past 24 months as compared to lifetime

Source: CS figure 1

Romosozumab (EVENITY, UCB)

Marketing authorisation	• For the treatment of severe osteoporosis in postmenopausal women at high risk of fracture • Granted by the European Medicines Agency in December 2019 • Contraindicated in people with previous myocardial infarction or stroke

Mechanism of action	• Monoclonal antibody that binds to and inhibits sclerostin
	• Inhibiting sclerostin:
	  • stimulates bone formation through promoting increased osteoblast number and activity
	  • reduces bone resorption through changing the expression of osteoclast mediators

Administration	• Subcutaneous injection: 210 mg once monthly for 12 months • After this transition to antiresorptive therapy is recommended
Price	• List price of romosozumab: £427.75 for each monthly dose consisting of 2 pre-filled pens • Cost for a fixed-duration 12-month treatment (based on list price): £5,133 • Patient access scheme discount proposed

Patient expert perspective

Living with osteoporosis

- Osteoporosis impacts every aspect of daily life including walking, eating and breathing, mobility. Pain can severely limit daily activities
- Physical changes, e.g., loss of height, shape of vertebrae. Can cause feelings of shame
- Psychological impact due to frequent fractures and fear of having fractures in future

Limited options for people with severe osteoporosis

- Range of treatments available but for some people these do not work very well and they continue to have fractures
- For some people current treatments (bisphosphonates) cannot be tolerated due to systemic side effects. Other options (denosumab, teriparatide) have limitations – need a new treatment

Romosozumab

- First new osteoporosis treatment in 10 years – offers potential step change and gives hope to people with osteoporosis
- Once-monthly injection more acceptable than daily injection regime of teriparatide
- 1-year treatment duration may be confusing, and association with cardiovascular events a concern

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"When you have a new fracture the pain is terrible. Then when pain is gone, the worst part is what shape you get into"

Clinical expert perspective

Aim of drug treatment for osteoporosis

- Main aims are to build bone strength, prevent future fractures and address pain
- Bisphosphonates, the most commonly used drugs for osteoporosis, reduce risk for major osteoporotic fractures by 33%, hip fractures by 33% and vertebral fractures by 55%. Risk reductions that are similar or higher than this would be clinically important

Current treatment options for people with severe osteoporosis

- Most people have oral bisphosphonates first-line, followed by parenteral treatments (denosumab and zoledronate) and then teriparatide if NICE criteria are met
- Systemic side effects are common over long-term and disease does not always respond. Around 25% of people having oral bisphosphonates cannot have them long-term
- Unmet need for people with high-risk disease: 1) for whom no drugs are suitable; 2) are at risk of vertebral/hip fractures; 3) are at risk of vertebral fractures and cannot have anabolic drugs

Romosozumab

- Only dual-action drug, shown to have better efficacy than oral bisphosphonates. No data vs teriparatide, but reduces hip fracture risk vs alendronate (unlike teriparatide)
- Would fit well into existing secondary care services; no investment needed
- Generally well tolerated, but some association with cardiovascular events

Decision problem (1/2)

	Final scope issued by NICE	Company	Justification if different
Population	Postmenopausal women with severe osteoporosis at high risk of fracture	Postmenopausal women with severe osteoporosis who are at high risk of fracture and have had a major osteoporotic fracture within past 24 months	**Company comment** Women with greatest unmet need and for whom romosozumab is expected to provide substantial clinical benefit **ERG comment** Population is narrower than the NICE scope
Intervention	Romosozumab	Romosozumab for 12 months, followed by sequential alendronate	**Company comment** Romosozumab is licensed as a 12-month course, followed by an antiresorptive

Source: ERG report table 2.1

Decision problem (2/2)

	Final scope issued by NICE	Company	Justification if different

Comparators	• Bisphosphonates
	  ○ alendronate, risedronate, ibandronate, zoledronate
	• Non-bisphosphonates
	  ○ denosumab, raloxifene, teriparatide
	• No active treatment
		• Alendronate the main comparator
		• Ibandronate omitted as comparator
		• All other comparators included as scenarios using network meta-analysis results
			Company comment
			No trials of ibandronate licensed dose were found to be included in the NMA for fracture outcomes
			ERG comment
			Comparators in line with NICE scope, except for exclusion of ibandronate

Outcomes	• Osteoporotic fragility fracture • Bone mineral density • Mortality • Adverse effects of treatment • Health-related quality of life	As per scope	**ERG comment** ARCH trial had median follow-up of 33 months. Likely insufficient to show survival difference

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NMA: Network meta-analysis

Source: ERG report table 2.1

Patient population and comparators

ERG: company's population is not aligned with NICE scope

NICE scope and marketing authorisation

- Postmenopausal women with severe osteoporosis at high risk of fracture (not further defined)

Company

- **ARCH trial population:** Postmenopausal women with severe osteoporosis who previously had a major osteoporotic fracture
- **Submission population:** Postmenopausal women with severe osteoporosis who previously had a major osteoporotic fracture within past 24 months ('imminent risk')
  - Several EU guidelines refer to very high or imminent risk as fracture within 24 months
  - Narrowing this, e.g., to 12 months, would exclude people with high unmet need

ERG comments

- Company's 'imminent risk' population is narrower than licensed population and ARCH trial
- Around [redacted]% of the ARCH population would fall into the submission population
- Most people in comparator studies of network meta-analyses align with ARCH trial rather than the submission
- Comparators may vary between the 'high-risk' and 'imminent risk' groups. Comparison of romosozumab vs. alendronate may not be fair/relevant in the imminent risk group
- For fair comparisons, company submission should focus on high-risk population from ARCH

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◉ Is the company's 'imminent risk' population appropriate for decision making?

Background: NICE clinical guideline and quality standard

NICE clinical guideline 146: assessing the risk of fragility fracture, updated 2017

Assessment of fracture risk should be considered in:

- Women aged 65 or more, men aged 75 or more
- Women aged less than 65 and men aged less than 75 in presence of risk factors

Methods of risk assessment:

- Estimate absolute risk when assessing risk of fracture using either FRAX or QFracture
- If results are in "region of an intervention threshold …", recalculate FRAX with BMD

NICE quality standard 149: osteoporosis, 2017

Statement 1: Assessment of fragility fracture risk:

- Adults who have had a fragility fracture or use systemic glucocorticoids or have history of falls have an assessment of fracture risk (FRAX or QFracture) (not age stratified as in CG146)

Statement 2: Starting drug treatment:

- Adults at high risk of fragility fracture are offered drug treatment to reduce fracture risk
- Intervention thresholds defined for FRAX:

Age (years)	40	45	50	55	60	65	≥70
10-year MOF probability (%)	5.9	6.0	7.2	9.4	12	16	20

BMD: Bone mineral density; MOF: Major osteoporotic fracture

Background: NICE bisphosphonates guidance (TA464 [2017, updated 2019])

- Oral bisphosphonates (alendronic acid, ibandronic acid and risedronate sodium) and IV bisphosphonates (ibandronic acid and zoledronic acid) are recommended, within their marketing authorisations, as options for treating osteoporosis in adults:
  - who are eligible for risk assessment as defined in NICE CG146 and NICE QS149
  - who have been assessed as higher risk of osteoporotic fragility fracture using methods recommended in NICE CG146 and NICE QS149
  - when bisphosphonate treatment is appropriate, taking into account risk of fracture, risk of adverse effects from bisphosphonates, and clinical circumstances and preferences
- Oral bisphosphonates found to be cost-effective for people with at least **1% fracture risk**
- IV bisphosphonates found to be cost-effective for people with at least **10% fracture risk**

Background: NICE non-bisphosphonates guidance (TA161 [2008] and TA204 [2010])

- Denosumab (DEN) recommended for **primary** prevention in postmenopausal women who cannot have alendronate and risedronate/etidronate, and who have necessary combination of T-score, age and no. of clinical risk factors for fracture (TA204, 2010)
- DEN, raloxifene (RLX, TA161, 2008, updated 2018), teriparatide (TPTD, TA161) recommended for **secondary** prevention in postmenopausal women cannot have alendronate and risedronate*, and who have the necessary combination of T-score, age and no. of risk factors/prior fractures

DEN: Primary prevention

	No. of independent clinical risk factors		
Age	0	1	2
50-54	NR	NR	NR
55-59	NR	NR	NR
60-64	NR	NR	NR
65-69	NR	-4.5†	-4.0
70-74	-4.5	-4.0	-3.5
≥75	-4.0	-4.0	-3.0

RLX: Secondary prevention

	No. of independent clinical risk factors		
Age	0	1	2
50-54	NR	-3.5	-3.5
55-59	-4.0	-3.5	-3.5
60-64	-4.0	-3.5	-3.5
65-69	-4.0	-3.5	-3.0
70-74	-3.0	-3.0	-2.5
≥75	-3.0	-2.5	-2.5

TPTD: Secondary prevention

	No. of prior fractures	
Age	≤2	>2
50-54	NR	-4.0
55-59	NR	-4.0
60-64	NR	-4.0
65-69	-4.0	-3.5
70-74	-4.0	-3.5
≥75	-4.0	-3.5

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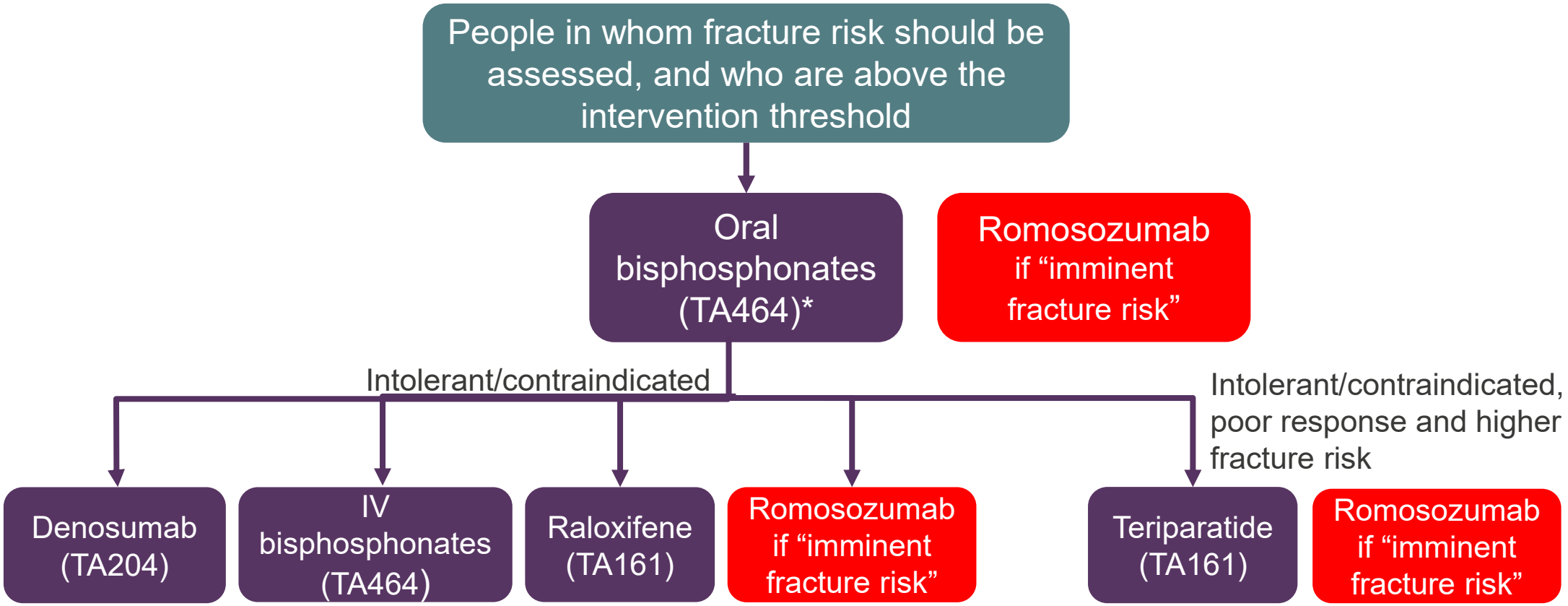
* Or etidronate, in the case of DEN; NR: Not recommended

† T-score: the standard deviation in BMD from that of a healthy adult

Osteoporosis treatment pathway



Incorporates:

- **NICE technology appraisal guidance**
- **Osteoporosis International Position paper (2020)**
- **UK consensus guideline (2020)**

◉ Where would romosozumab be used in the treatment pathway?
◉ Which are the most appropriate comparators in the imminent risk population?

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* National Osteoporosis Guideline Group Guidelines (2017): Alendronate/risedronate are first-line treatments in most cases; IV: Intravenous

Key trial: ARCH

Interventions	• Romosozumab for 12 months followed by open-label oral alendronate for at least 12 more months (n=2,046) • Oral alendronate for 12 months followed by open-label oral alendronate for at least 12 more months (n=2,047)

Key inclusion/ exclusion criteria	• Ambulatory postmenopausal women aged 55 to 90 who met at least 1 of:
	  • BMD T-score of –2.5 or less at total hip/femoral neck and:
	  • 1 or more moderate or severe vertebral fractures, or
	  • 2 or more mild vertebral fractures
	  • BMD T-score of –2.0 or less at total hip/femoral neck and:
	  • 2 or more moderate or severe vertebral fractures, or
	  • proximal femur fracture 3 to 24 months prior to randomisation
	• At least 1 hip that could be evaluated by dual X-ray absorptiometry
	• No recent use of drugs that affect bone metabolism

Primary outcomes	• Cumulative incidence of new vertebral fracture through month 24 • Cumulative incidence of clinical fracture at primary analysis (33 months)
Key secondary outcomes	• Incidence of fractures (non-vertebral, all fractures, new or worsening vertebral, major non-vertebral, hip, major osteoporotic fracture) • Percent change in BMD at lumbar spine, total hip, and femoral neck
Locations	[redacted] sites globally, including [redacted] people from [redacted] sites in the UK

NICE ◉ ***Would the ARCH inclusion criteria be used in the NHS?***

BMD: Bone mineral density; DXA: Dual-energy X-ray absorptiometry

FRAME and STRUCTURE trials

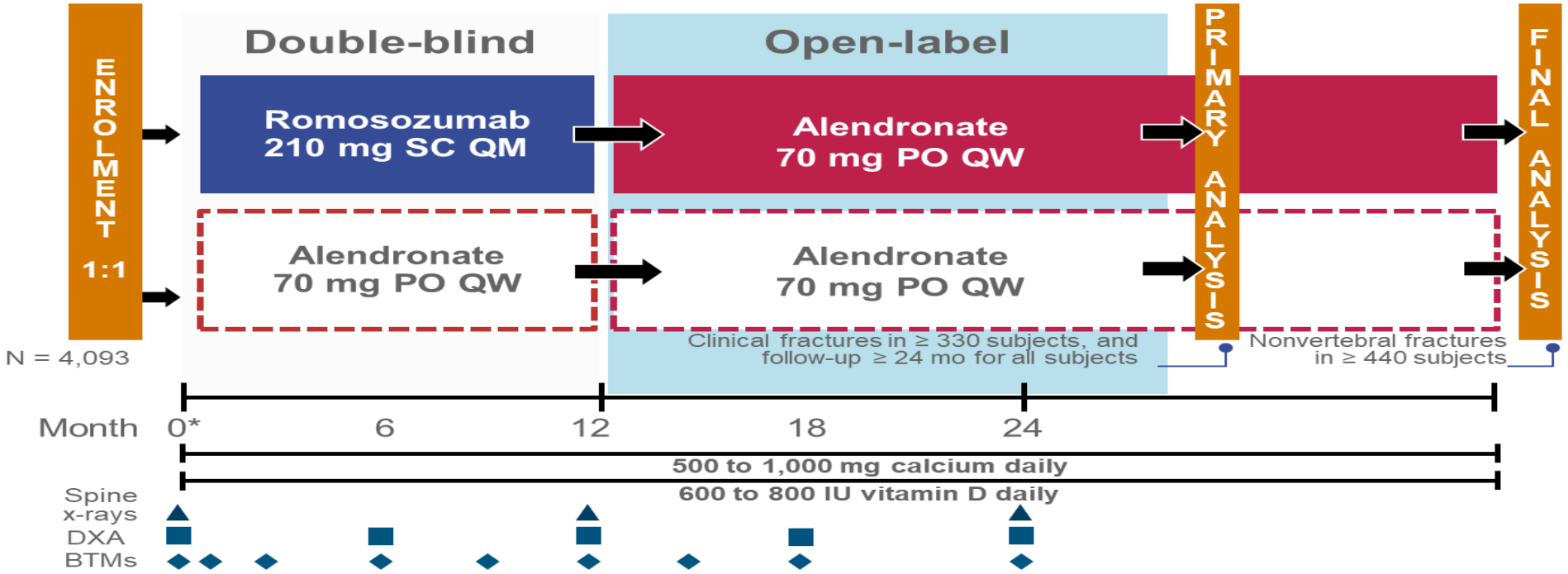
Supporting studies: not aligned with expected use in NHS practice

	FRAME	STRUCTURE
Study design	Multicentre, randomised, double-blind, placebo-controlled, parallel-group	
Population	Postmenopausal women with osteoporosis, aged 55–90	Postmenopausal women with osteoporosis transitioning from bisphosphonate therapy, aged 55-90 and with prior fragility fracture
Intervention(s)	Romosozumab (210 mg) once monthly SC for 12 months followed by open-label denosumab (60 mg) SC once every 6 months for 24 months (until study end)	Romosozumab (210 mg) once monthly SC for 12 months
Comparator(s)	Placebo once monthly SC for 12 months followed by open-label denosumab (60 mg) once every six months SC for 24 months (until study end)	Daily SC teriparatide (20 µg) for 12 months
Use in submission	Network meta-analysis Safety analysis	Network meta-analysis (BMD only) Safety analysis

BMD: Bone mineral density; SC: Subcutaneous

Source: Adapted from CS, Document B, Table 4

ARCH: event-driven trial design



- Event-driven trial that included initial screening and enrolment, and double-blind and open-label treatment periods. Primary analysis performed after all patients completed Month 24 visit, and at least 330 patients had confirmed clinical fracture events
- Median follow-up at time of primary analysis was 2.7 years (33 months)
- Final analysis when non-vertebral fracture events were confirmed for at least 440 patients

◉ Which antiresorptive treatments would likely be used after romosozumab in practice?

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BTM: Bone turnover marker; DXA: Dual-energy X-ray absorptiometry; IU: International unit; PO: Oral administration; QW: Once weekly; SC: Subcutaneous

Source: CS Figure 3

ARCH: Baseline characteristics

Baseline characteristic		ALN (n=2,047)	ROMO (n=2,046)
Mean age, years (standard deviation [SD])		74.2 (7.5)	74.4 (7.5)
Mean bone mineral density (BMD) T-score (SD)	Lumbar spine	–2.99 (1.24)	–2.94 (1.25)
	Total hip	–2.81 (0.67)	–2.78 (0.68)
	Femoral neck	–2.90 (0.50)	–2.89 (0.49)
Previous osteoporotic fracture at ≥45 years of age, no. (%)		2,029 (99.1)	2,022 (98.8)
Prevalent vertebral fracture, no. (%)		1,964 (95.9)	1,969 (96.2)
Grade of most severe vertebral fracture, no. (%)	Moderate	570 (27.8)	532 (26.0)
	Severe	1,321 (64.5)	1,369 (66.9)
Previous non-vertebral fracture at ≥45 years of age, no. (%)		770 (37.6)	767 (37.5)
Previous hip fracture, no. (%)		179 (8.7)	175 (8.6)
Mean FRAX major osteoporotic fracture risk (SD)		20.0 (10.1)	20.2 (10.2)
Prior use of osteoporosis medication, no. (%)	IV/oral bisphosphonates	130 (6.3)	136 (6.6)
	Denosumab	8 (0.4)	6 (0.3)
	Other	80 (4)	72 (3.5)

- **Company:** Time from prior major osteoporotic fracture at baseline not available
- **Clinical experts:** ARCH included people in whom anabolic treatment might be considered but excluded women who had recent osteoporosis therapies

◉ ***Are these baseline characteristics generalisable to NHS clinical practice?***

ALN: Alendronate; ROMO: Romosozumab; SD: Standard deviation

Source: Adapted from CS, Table 9

Romosozumab clinical effectiveness: summary

ARCH results

- *Compared with alendronate, romosozumab/alendronate significantly reduced the incidence of new vertebral fractures at month 24, and new clinical fractures at month 33 (primary analysis)*
- *Graphs for time to first clinical fracture and time to first non-vertebral fracture indicate that romosozumab efficacy may wane over time*
- *More people having romosozumab experienced serious cardiovascular events compared with alendronate*

Company network meta-analyses results

- *Romosozumab significantly better than or at least as good as most comparators, but most comparisons have high risk of bias*

BMD: Bone mineral density

ARCH: Key results from ITT population

Outcome	Timepoint	ALN (n=2,047)	ROMO (n=2,046)	Risk ratio/Hazard ratio/Mean difference	Used in model?
Primary outcomes				Point estimate (SE); (95% confidence interval [CI])	
Incidence of vertebral fracture	24 months	8.0%	4.1%	RR=0.50 [redacted] (0.38, 0.66)	✓
Incidence of clinical fracture	Primary analysis (33 months)	13.0%	9.7%	HR=0.73 [redacted] (0.61, 0.88)	✓
Key secondary outcomes				Point estimate (SE); (95% CI)	
Incidence of non-vertebral fracture	Primary analysis	10.6%	8.7%	HR=0.81 [redacted] (0.66, 0.99)	✓
Incidence of hip fracture		3.2%	2.0%	HR=0.62 [redacted] (0.42, 0.92)	✓
Incidence of major osteoporotic fracture		10.2%	7.1%	HR=0.68 [redacted] (0.55, 0.84)	✓
% change from baseline in bone mineral density (BMD)				Mean difference; (95% CI)	
Lumbar spine	36 months	7.8%	15.2%	MD=7.4 (6.84, 7.89)	✗
Total hip		3.5%	7.2%	MD=3.7 (3.29, 4.02)	✗
Femoral neck		2.4%	6.0%	MD=3.6 (3.18, 3.97)	✗

HR: Hazard ratio; ITT: Intent-to-treat; RR: Risk ratio; MD: Mean difference Source: Adapted from CS, Figure 6 and 7

ARCH results: time to first clinical/non-vertebral fracture

ERG: effects of romosozumab may wane after 42 months

Time to first clinical fracture

Time to first non-vertebral fracture

ERG comments

- Possible that effects of romosozumab wane as curves seem to converge between month 42 and 48, but based on smaller numbers of people which increases uncertainty

Clinical experts

- No long-term data available but based on mechanism of action and biochemical marker profile; would expect people to reach steady state

◉ *What is the anticipated continued treatment effect of romosozumab after it is stopped?*

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Source: CS Figures 7 and 9

Network meta-analysis (NMA): background

Head-to-head data not available for every comparator in NICE scope

Company

- Conducted NMAs to compare romosozumab/alendronate vs. bisphosphonates (alendronate, risedronate, ibandronate, zoledronate), teriparatide, denosumab and raloxifene
- Romosozumab significantly more effective than or equally effective as most comparators
- Romosozumab/alendronate showed [redacted] or [redacted] highest probability of being effective at reducing different fracture types and increasing bone mineral density

ERG comments

- In general, methods used to compare treatments directly/indirectly are appropriate and valid
- However, most studies had differences in mean age, ethnicity or rate of prevalent vertebral fractures, which could potentially be effect modifiers
- Individual studies rarely provided data consistently across timepoints. Some studies that were missing data at one timepoint had data from an earlier timepoint used instead
- Large differences in placebo arm fracture rates. Indicates population differences likely extending to unknown and unmeasured effect modifiers, increases risk of bias
- Comparisons between romosozumab, alendronate and placebo have low risk of bias. All other comparisons generally have high risk of bias

NMA (fracture outcomes) patient characteristics (1/2)

Study	Interventions	Age (years)	Ethnicity	Prevalent vertebral fractures (%)
ARCH	ROMO vs ALN	74	68% non-Hispanic	96
FRAME	ROMO vs PBO	71	60% non-Hispanic	18
ACTIVE	ABA vs PBO, TPTD	69	80% white	24
Dursum et al.,	ALN vs PBO	61	Not reported (NR)	NR
FIT I + II	ALN vs PBO	68	NR (USA study)	0
FIT I	ALN vs PBO	71	NR (USA study)	100
FOSIT	ALN vs PBO	63	NR (global study)	NR
Liberman et al.,	ALN vs PBO	64	NR (global study)	21
ROSE trial	ALN vs ZOL	68	99% white	NR
Bai et al.,	ZOL vs PBO	57	NR (Chinese study)	61
Chao et al.,	ZOL vs PBO	55	NR (Chinese study)	55
HORIZON-PFT	ZOL vs PBO	73	NR (global study)	63
ZONE	ZOL vs PBO	74	100% Japanese	100
VERT MN (EU)	RIS vs PBO	71	NR (all European)	>50
VERT-MN trial (NAm)	RIS vs PBO	69	NR (all USA)	80

ABA: Abaloparatide; ALN: Alendronate; PBO: Placebo; RIS: Risedronate; TPTD: Teriparatide; ZOL: Zoledronate

NMA (fracture outcomes) patient characteristics (2/2)

Study	Interventions	Age (years)	Ethnicity	Prevalent vertebral fractures (%)
ARCH	ROMO vs ALN	74	68% non-Hispanic	96
FRAME	ROMO vs PBO	71	60% non-Hispanic	18
Liu et al.,	RLX vs PBO	65	NR (Chinese study)	≤18
Lufkin et al.,	RLX vs PBO	68	NR (USA study)	NR
MORE	RLX vs PBO	74	NR	37
Morii	RLX vs PBO	65	100% Japanese	26
RUTH trial	RLX vs PBO	68	84% white	NR
Silverman et al.,	RLX vs PBO	66	87% white	56
FREEDOM	DEN vs PBO	72	NR (global study)	24
Hadji et al.,	TPTD vs PBO	71	80% white	90
Neer et al.,	TPTD vs PBO	70	99% white	100
VERO trial	TPTD vs RIS	72	98% white	100

NICE ◉ *Are the company's NMA results robust for decision making?*

ALN: Alendronate; DEN: Denosumab; PBO: Placebo; RIS: Risedronate; RLX: Raloxifene; TPTD: Teriparatide

NMA results: new vertebral fractures at 12, 24, 36 months

Romosozumab vs comparators based on fixed effects models, relative risk (95% CrI)

[redacted]

[redacted]

NICE ■ Statistically significant advantage ■ Numerical advantage ■ Numerical disadvantage

CrI: Credible interval; NMA: Network meta-analysis

ERG report figures 3.4 to 3.11

NMA results: non-vertebral fractures at 12, 24 and 36 months

Romosozumab vs comparators based on fixed effects models, relative risk (95% CrI)

NICE ■ Statistically significant advantage ■ Numerical advantage ■ Numerical disadvantage

CrI: Credible interval; NMA: Network meta-analysis

NMA results: hip fractures at 12, 24 and 36 months

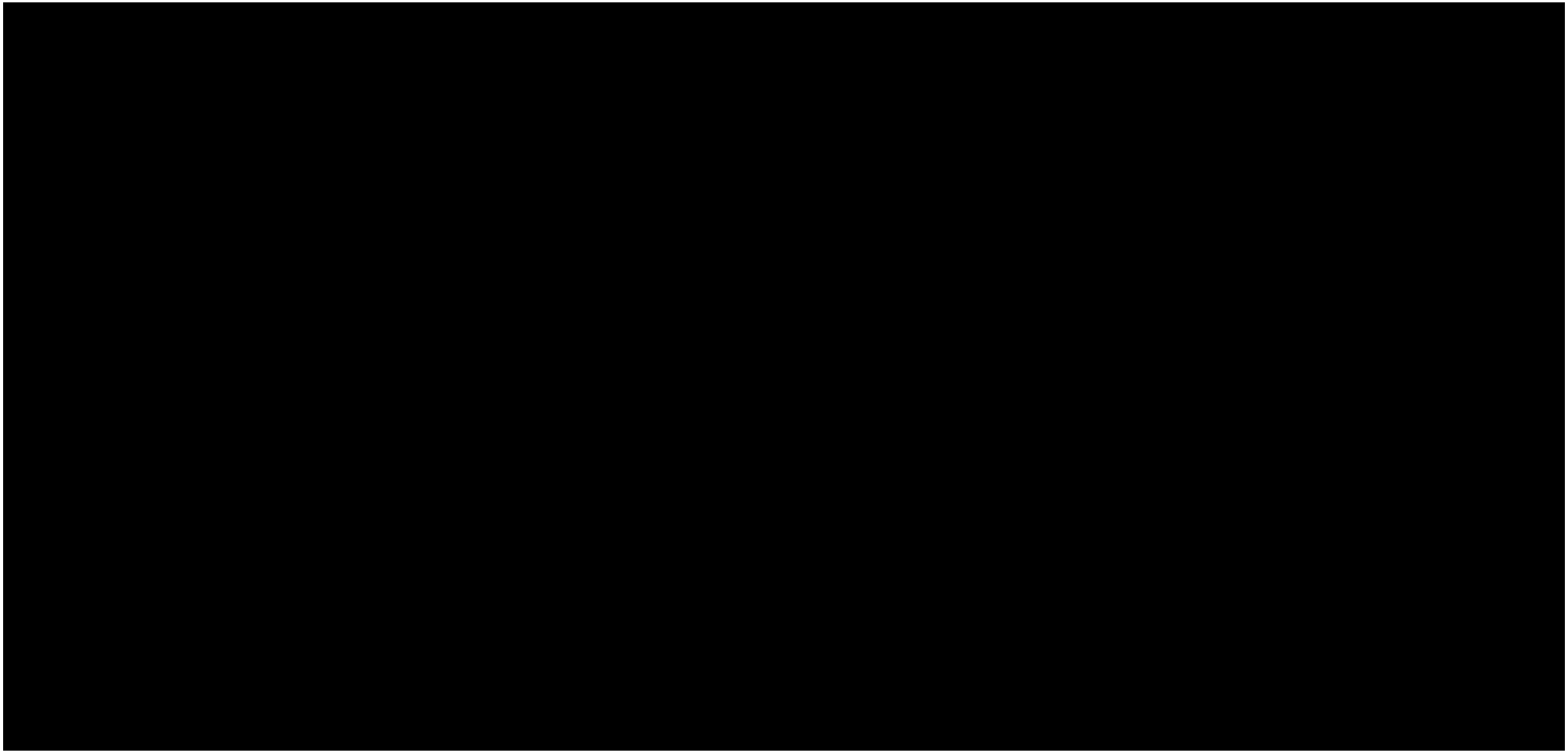
Romosozumab vs comparators based on fixed effects models, relative risk (95% CrI)

NICE ■ Statistically significant advantage ■ Numerical advantage ■ Numerical disadvantage

CrI: Credible interval; NMA: Network meta-analysis

NMA overall results: romosozumab significantly better than, or at least as good as, most comparators

Romosozumab vs comparators based on fixed effects models, relative risk (95% CrI)



Statistically significant advantage Numerical advantage Numerical disadvantage

NICE ◉ *Are the company's NMA results robust for decision making?*

CrI: Credible interval; NMA: Network meta-analysis

Romosozumab: serious cardiovascular events

More common in people having romosozumab than alendronate in ARCH, but no difference vs placebo in FRAME. Not included in company model

Cardiovascular events in ARCH trial

Event	Month 12		Primary analysis	
	ALN (n=2,014)	ROMO (n=2,040)	ALN/ALN (n=2,014)	ROMO/ALN (n=2,040)
Adjudicated serious cardiovascular event (n, %)	**38 (1.9)**	**50 (2.5)**	**122 (6.1)**	**133 (6.5)**
Cardiac ischemic event (n, %)	6 (0.3)	16 (0.8)	20 (1.0)	30 (1.5)
Cerebrovascular event (n, %)	7 (0.3)	16 (0.8)	27 (1.3)	45 (2.2)

Cardiovascular events in FRAME trial

Event	Double-blind period		36-month study period	
	Placebo (n=3,576)	ROMO (n=3,581)	Placebo (n=3,576)	ROMO (n=3,581)
Adjudicated serious cardiovascular event (n, %)	[redacted]	[redacted]	[redacted]	[redacted]
Cardiac ischemic event (n, %)	[redacted]	[redacted]	[redacted]	[redacted]
Cerebrovascular event (n, %)	[redacted]	[redacted]	[redacted]	[redacted]

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ALN: alendronate; ROMO: romosozumab

Source: Adapted from ERG report, table 3.10

Romosozumab cost effectiveness: summary

Model structure

- *Company uses a 5-state Markov microsimulation model. ERG could not fully critique model due to confidentiality issues with FRAX algorithm. Model also very slow to run*

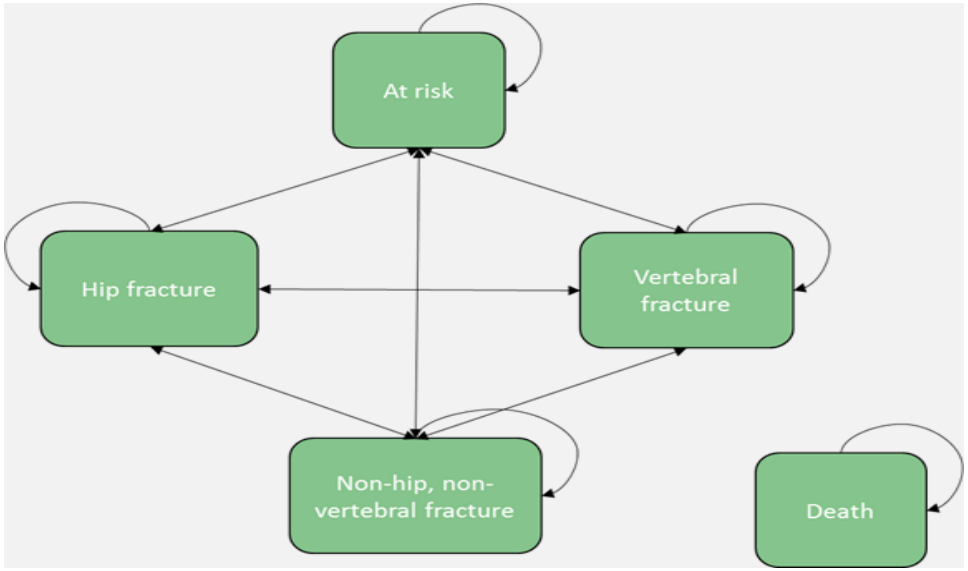
Assumptions and results

- *Differences between company and ERG for following assumptions have large impact on cost-effectiveness results:*
  - *Persistence on therapies*
  - *Utility multipliers*
  - *When excess mortality should be applied (which fracture types)*
- *Considerable difference between company base case vs alendronate (£16,600/QALY) and ERG base case (£483,750/QALY)*

QALY: Quality-adjusted life year

Company model structure

Structure	Markov microsimulation model with 5 health states
Horizon	Lifetime (100 years)
Cycle length	6 months
Discount rate	3.5% for both health and cost outcomes
Perspective	NHS and PSS



ERG comments

- Model structure appears appropriate. Company unable to provide VBA code password for full version of model due to confidentiality issues, but did provide some code separately
- All model calculations performed in background VBA code. ERG was unable to:
  - Verify that the code provided separately matched the code within the model
  - Step through the code in the model to understand the functionality of the code
  - Make any changes to the code
- Model extremely demanding on computational power. ERG could not run any PSAs
- Some issues identified, e.g., 0% of people had first NHNV fracture over model lifetime, while more than 0% of people had a second NHNV fracture. ERG could not identify cause

◉ Is the company model acceptable for decision making?

NHNV: non-hip, non-vertebral; PSA: Probabilistic sensitivity analysis : Adapted from CS Figure 13

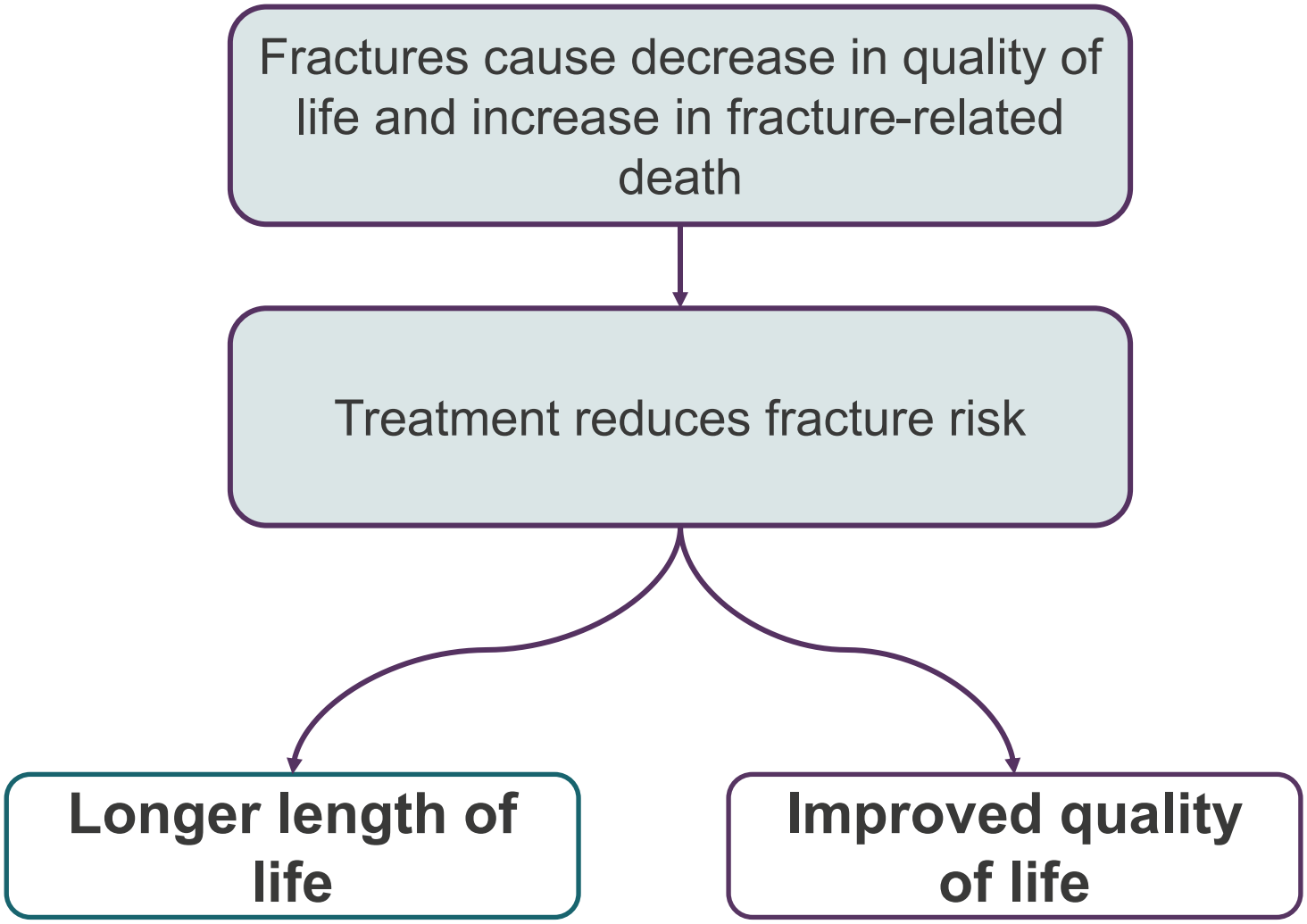
How company incorporated evidence into its model

Company uses clinical data from ARCH for model inputs

Input	Evidence Source
Baseline characteristics	Population from ARCH, but who have experienced a major osteoporotic fracture within past 24 months (FRAX risk: 30%)
Event probabilities	Clinical risk factors from ARCH incorporated into a FRAX-based algorithm incorporating imminent risk from Swedish registry
Utilities	Fracture utility multiplier from ICUROS study Gastrointestinal adverse event (AE) decrement from Davies et al., 2015
Costs	• Romosozumab costs: based on UCB's price for romosozumab; Other drug prices: BNF January 2021 drug tariff prices; Administration costs derived from SmPC for each drug • Gastrointestinal AE-associated costs from Davis et al. (2015), PSSRU, NHS Tariff Workbook 2020/21 • Fracture costs: inflated from UK study by Gutiérrez et al. (2011 and 2012) using UK GP database
Resource use	• Acute costs based on UK based study by Gutiérrez et al. • Long-term cost based on UK based study by Nanjayan et al.

BNF: British National Formulary; FRAX: Fracture risk assessment; GIAE: gastrointestinal adverse event; ICUROS: international costs and utilities related to osteoporotic fractures study; PSSRU: Personal Social Services Research Unit

Where do the QALYs come from in the model?



Key issues: cost-effectiveness

Issue	ICER impact
Patient population: which is appropriate for decision making?	
Comparators: which are most relevant?	
Duration of treatment effect: should this be limited (e.g., to 42 months after starting treatment)?	
Network meta-analyses: appropriate for decision making?	
Persistence: which rates should be used in the model?	
Fracture utility multipliers: robust for decision making?	
Excess mortality: which fracture types should this be attributed to?	
Fracture costs: should absolute or incremental fracture costs be used?	
Daily long-term care / administration costs: which should be used in the model?	
Cardiovascular adverse events: should these be included in the model?	

Key: Large impact  Small/moderate impact  Unknown impact 

Persistence with osteoporosis therapies

ERG: Company's approach to model persistence is inconsistent

Company

- Suboptimal persistence to osteoporosis medications frequent in clinical practice
- Assumed 90% of patients would complete 12 months of romosozumab based on ARCH
- Assumed persistence on alendronate after romosozumab would be 85% of denosumab persistence, as people completing romosozumab would likely be more persistent
- Used the following data sources for comparator persistence:
  - Alendronate alone, risedronate and raloxifene: Li et al. 2012
  - Denosumab: retrospective observational study using Swedish Prescribed Drug Register
  - Teriparatide and zoledronate: Swedish osteoporosis database

ERG comments

- Company's approach inconsistent between intervention and comparators
- ESCEO/IOF guidelines recommend using real-world data on medication adherence. However, this approach was only used for comparators
- Real-world persistence with romosozumab will be lower than in ARCH. Prefers to use lower value (80%), based on assumption in Swedish cost-effectiveness analysis (Söreskog et al.)
- Prefers using data from same study for alendronate persistence alone/after romosozumab
- Prefers to use data from same study (Morley et al. 2020) for persistence on alendronate, risedronate, raloxifene and denosumab. More recent than Li et al. and uses CPRD data

CPRD: Clinical Practice Research Datalink; ESCEO; European Society for Clinical and Economic Aspects of Osteoporosis, Osteoarthritis and Musculoskeletal Diseases; IOF: International Osteoporosis Foundation

Persistence: Li et al. and Morley et al.

Li et al. used for most bisphosphonates and RLX (company), Morley et al. used for most bisphosphonates, DEN, RLX (ERG)

Li et al. 2012 (Company preferred)	Morley et al. 2020 (ERG preferred)

• Used data from the UK General Practice Research Database (GPRD) from 1995 to 2008
• n=66,116 postmenopausal women who:
  ○ had an oral BP, oral raloxifene or oral strontium ranelate
  ○ were ≥50 years old or had early menopause
• Mean age of 71 years
• Used by assessment group in ID901, but not presented to committee
• **Company:** population less severe than submission (not required to have prior fracture). Likely alendronate persistence after romosozumab would be higher
• **ERG:** persistence estimates may not have been stable over study period
	• Used data from UK Clinical Practice Research Datalink (CPRD) from 2010 to 2015
	• n=72,256 postmenopausal women who received at least 1 prescription in primary care
	• Mean age of 74 years
	• **ERG:** preferred to use Morley et al. as it is a more recent study on persistence based on CPRD data. Used persistence estimates:
	  ○ from non-naïve patients having oral BPs for alendronate after romosozumab
	  ○ from naïve patients having oral BPs for alendronate alone

NICE

BP: bisphosphonate

Overview: company and ERG persistence assumptions

Treatment	Company's preferred estimates of persistence, month (%)							ERG preferred estimates of persistence, month (%)						
	Source	6	12	24	36	48	60	Source	6	12	24	36	48	60
ROMO	ARCH trial	90	90	0	0	0	0	Söreskog et al.	80	80	0	0	0	0
ALN after ROMO	Swedish drug register (85% of denosumab)	85	71	53	43	34	28	Morley et al. oral BPs, non-naïve	31	19	11	8	6	4
ALN	Li et al.	49	38	30	24	20	17	Morley et al. oral BP, naïve	62	51	38	29	24	18
TPTD	Swedish osteoporosis database	74	61	3	0	0	0	Swedish osteoporosis database	74	61	3	0	0	0
ZOL		100	100	42	28	18	12		100	100	42	28	18	12
DEN	Swedish drug register	100	83	62	50	40	33	Morley et al. DEN, naïve	64	55	36	28	22	16
RIS	Li et al.	50	38	28	21	16	12	Morley et al. oral BPs, naïve	62	51	38	29	24	18
RLX		45	33	26	21	17	14	Morley et al. SERM, naïve	53	42	33	25	24	22

ALN: alendronate; DEN: denosumab; RLX: raloxifene; ROMO: romosozumab; RIS: risedronate; SERM: selective estrogen receptor modulator; TPTD: teriparatide; ZOL: zoledronate

◉ Which persistence rates does committee prefer?

Source: ERG report table 4.12 and 4.13

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Which persistence rates does committee prefer?

Source: ERG report table 4.12 and 4.13

Fracture utility multipliers

Company:

- QoL impact of fractures modelled using multipliers applied to UK general population. E.g., first year hip fracture ([redacted]) x general population age 50 (0.849) = [redacted]
- Used utility multiplier for fractures from ICUROS combined with UK general population values instead of ARCH, as ARCH assessed QoL at pre-determined time points

Health state	Romosozumab (NICE ID3936)	Non-bisphosphonates (NICE ID901)	Bisphosphonates (NICE TA464)
First year after fracture			
Hip fracture	[redacted]	0.55	0.69
Vertebral fracture	[redacted]	0.68	0.57
Other NHNV fractures	[redacted]	0.805	0.87
Second and following years after fracture			
Hip fracture	[redacted]	0.86	0.85
Vertebral fracture	[redacted]	0.85	0.66
Other NHNV fractures	[redacted]	0.995	0.99

ERG comments: appropriate to use ICUROS multipliers; values differ from TA464 and ID901

- Multiplicative approach for impact of multiple chronic/acute fractures has been used in previous appraisals, although applied differently. Here, at most 2 multipliers could be applied
- Unable to test impact of methodology for applying multiple fractures, and company also declined to add an option for a reduced duration of chronic multipliers in the model

◉ Are the company's utility multipliers appropriate for decision making?

ICUROS: International Costs and Utilities Related to Osteoporotic Fractures Study; QoL: quality of life

Excess mortality by fracture type

Company

- All-cause mortality based on UK Life Tables 2012-14
- Once people have a fracture, increased relative risk vs non-fractured population is applied to all-cause mortality. 30% of overall increased relative risk applied in model, as an estimate of the excess mortality directly attributable to fracture (rather than general frailty)
  - E.g., relative mortality risk in year 1 after hip fracture: 9.79 x 30% = 2.9 RR used in model
- 30% figure aligned with ESCEO/IOF recommendations
- Modelled excess mortality after hip, vertebral and other (NHNV) fractures

ERG comments

- Unclear why company used 2012-14 Life Tables. Preferred to use 2017-19 in its base-case
- ESCEO/IOF recommendations suggest that only the excess mortality of hip and vertebral fractures should be included, as there is not yet enough evidence regarding NHNV fractures
- However, due to lack of clinician consensus on including excess mortality after vertebral fractures, ERG applied excess mortality after hip fractures only

ESCEO/IOF guidance

- Recommendations: excess mortality after hip fracture only
- Minimum criteria for economic evaluation: excess mortality after hip and vertebral fractures
- Scenarios with and without excess mortality after vertebral fractures recommended

◉ After which fracture types should excess mortality be modelled?

NICE

ESCEO: European Society for Clinical and Economic Aspects of Osteoporosis, Osteoarthritis and Musculoskeletal Diseases; IOF: International Osteoporosis Foundation; NHNV: non-hip, non-vertebral

Daily long-term care costs

Company:

- Hip fractures are associated with increased admission to long-term care facilities
- Long-term costs were based on ESCEO/IOF recommendations for the conduct of economic evaluations in osteoporosis and in line with TA464 (bisphosphonates)
- Daily cost of long-term care (**£112**) in nursing home based on EU study updated using CPI, based on probability of being discharged to institutional care

ERG comments:

- TA464 costs for long-term care based on:
  - equal % of people discharged to long-term care go to nursing/residential care homes
  - private sector costs are applicable (private sector provides 78% of places)
  - 36% of care is self-funded
- Used unit costs based on PSSRU 2020; estimated **£67** daily cost of long-term care

◉ What daily long-term care cost does committee prefer?

CPI: consumer price index; ESCEO: European Society for Clinical and Economic Aspects of Osteoporosis, Osteoarthritis and Musculoskeletal Diseases; IOF: International Osteoporosis Foundation ;PSP: patient support programme; PSSRU: Personal Social Services Research Unit

Administration costs

Company:

- Plans to set up a Patient Support Programme (PSP) which will include homecare service, an adherence support program, and training of injection techniques
- So applied no administration costs for romosozumab and alendronate as it is given orally, while applied administration costs for denosumab and zoledronate
- For denosumab and zoledronate administration costs values at £9.50 and £160 respectively based on PSSRU 2020

ERG comments

- At clarification, requested to include administration costs for romosozumab and all relevant comparators
- In response, company provided scenario with 12 nurse visits per year (each for £9.50) and 365 visits per year for teriparatide
- ERG assumed no PSP for its base case and performed the following scenario analyses:
  - no administration costs are applied for romosozumab (PSP in place)
  - no administration costs are applied with 90% persistence with romosozumab (likely that the PSP would improve romosozumab persistence)

NHS England: proposed PSP should not be taken into account in appraisal, as it is unlikely to be approved as part of a commercial arrangement

Fracture costs

Company

- Included first-year costs of hip, vertebral and NHNV fractures in model based on UK study by Gutiérrez et al., updated to 2020 using the consumer price indices (CPI)
- Subsequent years based on Davies et al. 2016 and updated to 2020 using the CPI, but these were only applied to hip and vertebral fractures not NHNV

Source	Hip fracture (£)	Clinical vertebral fracture (£)	NHNV fractures (£)
Costs during first year after fracture			
Gutiérrez et al (company preferred)	13,203	2,897	2,131
Gutiérrez et al (ERG preferred)	5,369	1,465	877
Costs during subsequent years			
Davies et al	115	361	-

ERG comments

- Company's first-year costs based on total costs from Gutiérrez et al., which also provide incremental costs relative to matched control
- More appropriate to include incremental costs in base-case since these are the costs specific to the fracture. Similar approach used in TA464
- Acknowledges that incremental costs do not include rehabilitation costs which were included in total cost for hip fracture used by company. TA464 did not include rehabilitation costs

NICE ◉ ***Should total or incremental fracture costs be used?***

NHNV: non-hip, non-vertebral

Cardiovascular adverse events

Excluded from company base case

Company

- Romosozumab is contraindicated for people with previous myocardial infarction or stroke
- Excluded cardiovascular (CV) adverse events from economic analyses, in line with ID901

Cardiovascular events in ARCH trial	Month 12		Primary analysis	
	ALN (n=2,014)	ROMO (n=2,040)	ALN/ALN (n=2,014)	ROMO/ALN (n=2,040)
Adjudicated serious CV event (n, %)	38 (1.9)	50 (2.5)	122 (6.1)	133 (6.5)

ERG comments:

- Unclear if all CV adverse events (AEs) occurred in people with history of myocardial infarction or stroke. If not then exclusion of CV AEs is inappropriate – ERG preferred to include these in its base case
- At clarification, requested company to include CV AEs in model. In response company provided a scenario using relative risk of a CV AE based on ARCH ([redacted] during the first [redacted] years after randomisation, compared with alendronate)
  - Multiplier for quality of life impact of 0.91 in first year, and 0.95 in following years
  - Identified costs of CV adverse events based on a systematic review by Ryder et al. 2019
- ERG also provided scenario excluding CV adverse events from ERG base case

NICE

◉ Should cardiovascular events be included in the model?

Duration of treatment effect

ERG: effects of romosozumab may wane after 42 months

Company

- Assumed the duration of treatment effect is maintained for 5 years (60 months)
- After this, a dynamic offset (linear waning) of treatment effect is assumed for another 5 years
- At year 11, assumed no treatment effect

ERG comments

- Possible that effects of romosozumab wane as curves seem to converge between month 42 and 48, but based on smaller numbers of people which increases uncertainty
- Provides a scenario assuming treatment waning starts at 48 months followed by a dynamic offset (linear waning) of the treatment effect for 12 months
- Used waning assumption to consider an effect between sequential alendronate and alendronate alone as assumed by the company

◉ Should the duration of treatment effect for romosozumab be limited (e.g., to 42 months after starting treatment)? How should this be applied in the model?

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Summary of company/ERG base cases

Assumption		Company	ERG
Persistence on romosozumab		90%	80%
Persistence on alendronate	After ROMO	85% of persistence with denosumab	Morley et al. 2020 persistence with oral BP in non-naïve people
	Alone (as comparator)	Li et al. 2012	Morley et al. 2020 persistence with oral BP in naïve people
Excess mortality after fracture		For hip, vertebral, NHNV fractures	For hip fractures only
Daily costs of long-term care		£112	£67
Costs associated with fractures	Hip	£13,203	£5,369
	Vertebral	£2,897	£1,465
	NHNV	£2,131	£877
Cardiovascular events		Not included	Included
ROMO administration costs		Not included (PSP in place)	Included (PSP not in place)
Frequency of physician visits		Once per year	Twice per year
General population mortality		2012-2014 Life tables	2017-2019 Life tables

BP: bisphosphonate; NHNV: non-hip, non vertebral; PSP: patient support programme; ROMO: romosozumab

Source: ERG report table 6.1

Company and ERG base-case deterministic cost-effectiveness results

Technologies	Total			Incremental			ICER (£/QALY)
	Costs (£)	Life-years	QALYs	Costs (£)	Life-years	QALYs	
Company base-case* (including PSP)							
ALN	[redacted]	10.014	[redacted]	[redacted]	0.031	[redacted]	16,660
ROMO/ALN	[redacted]	10.045	[redacted]				
Company base-case* (excluding PSP)							
ALN	[redacted]	-	[redacted]	[redacted]	-	[redacted]	17,680
ROMO/ALN	[redacted]	-	[redacted]				
ERG base-case*							
ALN	[redacted]	10.050	[redacted]	[redacted]	-0.002	[redacted]	483,750
ROMO/ALN	[redacted]	10.048	[redacted]				

ALN: alendronate; ROMO/ALN: romosozumab/ alendronate; ICER: incremental cost-effectiveness ratio; QALYs: quality-adjusted life years; PSP: patient support programme

- Due to inclusion of serious cardiovascular events in the ERG base, the incremental life years gained are negative
- Very small gain in incremental QALYs, substantially increased the ERG base-case ICER

NICE

* Results include PAS discount for romosozumab but do not include confidential commercial discounts for comparators

Persistence: ERG scenario analysis

No	Scenario	Incremental		Deterministic ICER vs alendronate (£/QALY)
		Costs	QALYs	
1	**Company base case:** • ROMO: 90% • ALN after ROMO: 85% of denosumab • ALN as comparator: Li et al. 2012	[redacted]	[redacted]	16,660
2	**ERG base case:** • ROMO: 80% • ALN after ROMO: Morley et al. oral BPs non-naïve • ALN as comparator: Morley et al. oral BPs naïve	[redacted]	[redacted]	483,750
3	Morley et al. pooled persistence (naïve and non-naïve) with oral BPs	[redacted]	[redacted]	81,333
4	ERG base case + 90% romosozumab persistence	[redacted]	[redacted]	267,533
5	ROMO persistence per ERG base-case; comparators per company base-case	[redacted]	[redacted]	40,315
6	Persistence based on ARCH data for romosozumab and alendronate	[redacted]	[redacted]	ROMO dominated
7	ROMO persistence = teriparatide persistence	[redacted]	[redacted]	ROMO dominated

ALN: alendronate; RLX: raloxifene; RIS: risedronate; ROMO: romosozumab; ICER: incremental cost-effectiveness ratio; QALYs: quality-adjusted life years

ERG scenarios: impact of other assumptions on ERG base case

Scenario (vs alendronate, unless indicated)	Incremental		Deterministic ICER vs alendronate or TPTD (£/QALY)
	Costs (£)	QALYs	
ERG base case	[redacted]	[redacted]	483,750
Fracture utility multipliers			
TA464 multiplier	[redacted]	[redacted]	258,000
ID901 multiplier	[redacted]	[redacted]	552,857
Excess mortality			
Hip and vertebral	[redacted]	[redacted]	355,273
Hip, vertebral and NHNV	[redacted]	[redacted]	354,545
Patient support programme (romosozumab administration costs)			
No admin. costs for romosozumab	[redacted]	[redacted]	471,250
No admin. costs + 90% ROMO persistence	[redacted]	[redacted]	260,533
Treatment effect waning			
4 years full effect then 1 year waning	[redacted]	[redacted]	554,714
Cardiovascular adverse events			
No cardiovascular events	[redacted]	[redacted]	310,917
Imminent risk removed	[redacted]	[redacted]	ALN dominates
ROMO/ALN vs TPTD	[redacted]	[redacted]	ROMO/ALN dominates

Innovation

Company

- Romosozumab is a novel treatment that both stimulates bone formation and decreases bone resorption
- Provides a clear advantage over current treatments by rapidly increasing bone formation
- Long-term maintenance of increased bone mineral density will benefit patients and reduce their risk of future fracture and reduce resources and cost associated with fragility fractures

Patient experts

- First new osteoporosis treatment in 10 years – offers potential step change and gives hope to people with osteoporosis

Equality

Patient organisation

- Romosozumab is licensed for postmenopausal women, this should not prevent the use of romosozumab in men, as the benefits of treatment are likely to be similar

◉ Is romosozumab innovative for treating severe osteoporosis?
◉ Are there any additional benefits with romosozumab that have not been captured?

Back up slides

Background: FRAX

Fracture risk assessment tool

- Calculates 10-year probability of hip fracture + major osteoporotic fracture
- Derived from individual patient-level data – includes femoral neck bone mineral density (BMD)
- UK model based on data using observational study of 15,000 adults in UK, observational study in Sweden and UK mortality and epidemiology data
- Risks included in the model: Age, Sex, Weight, Height, Previous fracture, Parental hip fracture, Current smoking, Glucocorticoid use, Rheumatoid arthritis, 2° osteoporosis, alcohol consumption, femoral neck BMD

- FRAX is used more widely in the UK than QFracture, another risk assessment tool that does not incorporate BMD as a risk factor
- Neither FRAX or QFracture consider recency of prior fracture in assessing fracture risk
- Generally, an individual will have a higher risk with FRAX than QFracture

Company's model functionality and usability

ERG's ability to evaluate the model functionality was hindered

Background

- ERG's ability to step through and evaluate the model functionality was hindered as all the calculations were done in background VBA code
- VBA code was password protected and the company were unable to make the password available to the ERG due to confidentiality issues with FRAX algorithm
- Outside of the VBA code only input parameters and hardcoded results were available
- After clarification, the company provided most of the VBA code but the ERG was unable to make any changes to assumptions beyond input parameters

ERG comments

- Model review would be facilitated if calculations were performed in the model worksheets, instead of being hard coded in VBA
- Difficult to validate the model as it is extremely demanding regarding the computational power needed to run within a reasonable time
- Full evaluation of the model and the assumptions included could not be performed without access to the VBA code within the model
- Suggest the company conduct an analysis to estimate the minimal PSA loop sizes that would provide reliable results in a minimum running time and to re-consider the programming of the model in order to make it computationally more efficient

NICE ◉ ***Is company model acceptable for decision making?***

FRAX: Fracture risk assessment;PSA: probilistic sensitivity analysis; VBA: visual basic for applications

ARCH: Clinical effectiveness summary- secondary outcomes

Secondary outcomes		Alendronate (N=2,047)	Romosozumab (N=2,046)	HR (SE) (95%CI)
Incidence of non-vertebral fracture primary analysis		217/2047	178/2046	HR=0.81 (0.10); (0.66,0.99)
BMD outcomes	Months	N, LS mean (SE)	N, LS mean (SE)	Mean difference
Lumbar spine	12	[redacted]	[redacted]	8.7 (8.31, 9.09)
	24	[redacted]	[redacted]	8.1 (7.58, 8.57)
	36	[redacted]	[redacted]	7.4 (6.84, 7.89)
Total hip	12	[redacted]	[redacted]	3.3 (3.03, 3.60)
	24	[redacted]	[redacted]	3.3 (3.03, 3.60)
	36	[redacted]	[redacted]	3.7 (3.29, 4.02)
Femoral neck	12	[redacted]	[redacted]	3.2 (2.90, 3.54)
	24	[redacted]	[redacted]	3.8 (3.40, 4.14)
	36	[redacted]	[redacted]	3.6 (3.18, 3.97)

CI: confidence interval; BMD: bone mineral density; HR: hazard ratio; LS: least squares; N: number of people RR: risk ratio; SE: Standard error

- People treated with romosozumab was associated with statistically significantly greater increase in BMD from baseline compared to alendronate (adjusted p<0.001), which was maintained until month 36

Source: Adapted ERG report table 3.9

ARCH: Clinical effectiveness summary- secondary outcomes

Secondary outcomes Incidence	Months	Alendronate (N=2,047)	Romosozumab (N=2,046)	RR (SE) (95%CI) HR (SE) (95%CI)
New vertebral fracture	12	85/1703 (5.0%)	55/1696 (3.2%)	RR= 0.64 [redacted]; (0.46, 0.89)
Incidence of clinical fracture	12	110/2047 (5.4)	79/2046 (3.9)	HR= 0.72 [redacted] (0.54, 0.96)
	24	[redacted]	[redacted]	[redacted]
Incidence of non-vertebral fractures	12	95/2047 (4.6)	70/2046 (3.4)	HR= 0.74 [redacted] (0.54, 1.01)
	24	[redacted]	[redacted]	[redacted]
Incidence of clinical vertebral fracture	12	18/2047 (0.9)	10/2046 (0.5)	HR= 0.56 [redacted] (0.26, 1.22)
	24	44/2047 (2.1)	18/2046 (0.9)	HR= 0.41 [redacted] (0.24, 0.71)
Incidence of hip fractures	12	22/2047 (1.1)	14/2046 (0.7)	HR= 0.64 [redacted] (0.33, 1.26)
	24	[redacted]	[redacted]	[redacted]
	Primary analysis	66/2047 (3.2)	41/2046 (2.0)	HR= 0.62 [redacted] (0.42, 0.92)

CI: confidence interval; HR: hazard ratio; RR: risk ratio;SE: Standard error

- People treated with romosozumab had a lower incidence of new vertebral, clinical fracture, non-vertebral at 12 and 24 months and hip fractures at 12, 24 and primary analysis

Source: Adapted from ERG report table 3.9

ARCH: Clinical effectiveness summary - secondary outcomes

Secondary outcomes incidence		Alendronate (N=2,047)	Romosozumab (N=2,046)	Hazard ratio (SE) (95% CI)
Major nonvertebral fractures	12 months	88/2047 (4.3)	59/2046 (2.9)	HR= 0.67 [redacted] (0.48, 0.94)
	Primary analysis	196/2047 (9.6)	146/2046 (7.1)	HR= 0.73 [redacted] (0.59, 0.90)
Major osteoporotic fractures	12 months	85/2047 (4.2)	61/2046 (3.0)	HR= 0.72 [redacted] (0.52, 1.01)
	Primary analysis	209/2047 (10.2)	146/2046 (7.1)	HR= 0.68 [redacted] (0.55, 0.84)
All osteoporotic fractures	12 months	189/2047 (9.2)	134/2046 (6.5)	HR= 0.71 [redacted] (0.57, 0.88)
	Primary analysis	392/2047 (19.1)	266/2046 (13.0)	HR= 0.65 [redacted] (0.56, 0.76)

CI: confidence interval; HR: hazard ratio; SE: Standard error

Source: Adapted from ERG report table 3.9

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