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Romosozumab for osteoporosis in men

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LAY SUMMARY

Osteoporosis is a chronic condition where the bones lose their strength. It is characterised by low bone mass and deterioration of the bones which leads to the increased risk of broken bones ('fractures'). Osteoporosis is often called a 'silent disease' because there are no symptoms or pain until a fracture occurs. When fractures do occur they can cause substantial pain and disability and can be life altering for some patients, particularly those with hip fractures. One in two women and one in five men over the age of 50 experience fractures, mostly as a result of low bone strength caused by osteoporosis.

Romosozumab arose from a genetic discovery that revealed the body's own natural ability to increase bone strength. It is a treatment which aims to block the activity of the protein sclerostin. This diminishes bone breakdown and removal and stimulates bone formation, thereby increasing bone strength. The effectiveness and safety of romosozumab for the treatment of osteoporosis in men has been studied in a phase III clinical trial. The study showed that romosozumab given by injection monthly for a 12 month period significantly increased the formation of new bones, reducing the risk of a fracture. Romosozumab was also found to be safe with no significant adverse effects.

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TARGET GROUP

- Osteoporosis in men at high risk of fracture (those aged 55 years and above) – first line

TECHNOLOGY

DESCRIPTION

Romosozumab (Evenity; AMG-785; CDP-7851) is an anti-sclerostin monoclonal antibody under development for the treatment of bone-related conditions, which include osteoporosis in postmenopausal women and osteoporosis in men.[1]

Romosozumab is a new molecular entity (NME) that is designed to work by binding to, and inhibiting the activity of the protein sclerostin. Sclerostin, produced and secreted by the osteocyte (bone cells), is a protein that inhibits bone formation. The inhibition of sclerostin by romosozumab has a dual effect on bone, increasing bone formation and decreasing bone resorption.[2]

In a phase III clinical trial, romosozumab was administered to men aged 55 to 90 years through subcutaneous injection (210mg) monthly for 12 months and was compared with a matched placebo for the duration of the 12-month treatment period.[3, 4] The results demonstrated a statistically significant increase in bone mineral density (BMD) at the lumbar spine (primary endpoint) and at the femoral neck and total hip (secondary endpoint).

Romosozumab is also currently under development for the treatment of osteoporosis in premenopausal women and was also studied (phase II) for the treatment of fracture healing but was not advanced to phase III.[5]

Romosozumab does not currently have Marketing Authorisation in the EU for any indication.

INNOVATION and/or ADVANTAGES

If licenced, romosozumab will offer an additional treatment option for osteoporosis in men as a first line therapy or in combination with other therapies. It offers the advantage of having a more specific and targeted mechanism of action than those of currently marketed drugs,[6] in addition to its lower frequency of administration (once a month by subcutaneous injection).[2]

Most current pharmacological agents for osteoporosis are targeted at improving BMD and reducing fragility fractures, either by increasing bone formation (bone stimulatory or anabolic agents) or decreasing bone resorption (antiresorptive agents).[7] The majority of currently approved agents for osteoporosis such as bisphosphonates (e.g. alendronates and risedronate) and denosumab are antiresorptive agents.[6, 7]

Rosomozumab has been shown to have both bone stimulatory and antiresorptive properties,[8, 9] and has been specifically tested in clinical trials in men with osteoporosis, whereas most current treatments have only been tested in postmenopausal women.[10] Comparative studies in women showed that romosozumab increased BMD in the spine by 11.3%, compared with a 7.1% increase with

teriparatide (Forteo) and also performed much better than alendronate (Fosamax), a bisphosphonate medication that increased spinal bone density by 4.1%.[9]

DEVELOPER

UCB and Amgen

AVAILABILITY, LAUNCH or MARKETING

Phase III clinical trials on romosozumab for osteoporosis in men have been completed.

PATIENT GROUP

BACKGROUND

Osteoporosis is a systemic skeletal condition that causes bones to weaken and become less dense, making them fragile and increasing the risk of bone fractures.[11] Osteoporosis is generally perceived as a women's disease (as postmenopausal osteoporosis),[12] but it also affects men and can have more severe consequences, for example, mortality risk after hip and femoral fracture is higher in men than women.[8]

Osteoporosis in men is an underdiagnosed and undertreated condition that should be considered as a serious public health concern.[8] Overall, one in five men over the age of 50 will have an osteoporosis related fracture and this is greater than the likelihood of developing prostate cancer.[12] Osteoporosis in men occurs slowly with age with bone loss beginning by the sixth grade at an average rate of 0.5% to 1.0% per year.[13]

Bone tissue continuously undergoes a process of bone deposition (build-up) and resorption (breakdown). In osteoporosis, there is an imbalance that leads to increased bone resorption and reduced bone deposition which leads to bone loss and increased risk of fractures.[8] Hormonal changes during aging are a primary cause of bone loss in men,[8] but other associated risk factors include prolonged exposure to certain medications (e.g. steroids), certain chronic diseases, vitamin D deficiency and lifestyle factors (e.g. smoking, excessive alcohol consumption, poor diet, and lack of physical activity).[12]

Diagnosis of osteoporosis in men is similar to that in women and is based on the measurement of BMD criteria that defines osteoporotic patients as those whose BMD is lower than -2.5 standard deviations (T-score) with respect to a reference population and the presence of one or more fragility fractures.[14] More recent tools such as the FRAX management algorithm has been made to identify men who should benefit from treatment.[15] Undiagnosed and untreated osteoporosis in men is associated with an increased risk of bone fractures, disability and mortality.

CLINICAL NEED and BURDEN OF DISEASE

In 2010, it was estimated that there were approximately 3.2 million people in the UK with osteoporosis, 679,424 of whom were male.[16] Approximately 1 in 5 men aged over 50 in the UK will break a bone because of poor bone health.[17]

An estimated 536,000 new fragility fractures are sustained in the UK each year, approximately 36% of which occur in men. In 2011, fragility fractures were estimated to cost £2.3 billion in the UK, a burden expected to increase to more than £6 billion by 2036.[17]

The majority of these costs relate to hip fracture, which nearly always results in hospitalisation, and causes around 1,100 deaths each month in the UK.[17] Men with hip fractures have a mortality rate two to three times higher than women.[18] Commonly used treatments for osteoporosis take longer than one year to reduce clinical fracture risk and there is currently only one bone-forming agent available in the UK, requiring daily injections.[19]

The population of men with osteoporosis likely to be eligible to receive romosozumab could not be estimated from available published sources. However, this may include those who have already experienced a fragility fracture, as these patients are at a higher risk for further fractures, particularly in the 12 to 24 months following the initial fracture.

PATIENT PATHWAY

RELEVANT GUIDANCE

NICE GUIDANCE

NICE guidance relevant to the technology and/or patient group – published and in development:

- NICE technology appraisal in development. Biphosphonates for preventing osteoporotic fragility fractures (including a partial update of NICE technology appraisal guidance 160 and 161) (ID782). Expected date of issue to be confirmed.
- NICE technology appraisal in development. Osteoporosis (prevention) – bisphosphonates (including a partial review of TA160, TA161) [ID782]. Expected date of issue to be confirmed.
- NICE technology appraisal. Percutaneous vertebroplasty and percutaneous balloon kyphoplasty for treating osteoporotic vertebral compression fractures (TA279). April 2013.
- NICE technology appraisal. Denosumab for the prevention of osteoporotic fractures in postmenopausal women (TA204). October 2010.
- NICE technology appraisal. Alendronate, etidronate, risedronate, raloxifene, strontium ranelate and teriparatide for the secondary prevention of ostoporotic fragility fractures in postmenopausal women (amended) (TA161). October 2008.
- NICE technology appraisal. Alendronate, etidronate, risedronate, raloxifene and strontium ranelate for the primary prevention of osteoporotic fragility fractures in postmenopausal women (TA160). October 2008.
- NICE clinical guideline. Osteoporosis: assessing the risk of fragility fracture (CG146). August 2012. (Updated February 2017).
- NICE quality standard. Osteoporosis (QS149). April 2017.

NHS ENGLAND and POLICY GUIDANCE

- NHS England. The National Service Framework for Older People (2001).
- NHS England. 2013/14 NHS Standard Contract for Specialised Endocrinology Services (Adult). A03/S/a.
- NHS England. 2013/2014. NHS Standard Contract for Specialised Rheumatology Services (Adult). A13/S/a.

OTHER GUIDANCE

- National Osteoporosis Guideline Group, Guideline for the diagnosis and management of osteoporosis in postmenopausal women and men from the age of 50 years in the UK. Updated March 2014. Available from: http://www.shef.ac.uk/NOGG/NOGG_Pocket_Guide_for_Healthcare_Professionals.pdf
- National Osteoporosis Society. Effective Secondary Prevention of Fragility Fractures: Clinical Standards for Fracture Liaison Services. April 2015. Available from http://www.nos.org.uk/standards

CURRENT TREATMENT OPTIONS

Treatments have been less extensively evaluated in men with osteoporosis than in women, though there is no evidence that skeletal metabolism in men differs fundamentally from that of women.[18] In the context of strategies for treating individuals at high risk of fracture, no distinction is made between prevention and treatment. A range of pharmaceutical interventions has been shown to be effective in reducing fracture risk in osteoporosis when given with calcium and vitamin D.[20, 21]

According to the National Osteoporosis Guideline Group (2017),[21] alendronate and risedronate (bisphosphonates) are first line treatments in men. Where these are contraindicated or not tolerated, zoledronic acid or denosumab provide the most appropriate alternatives, with teriparatide as an additional option.

EFFICACY and SAFETY

Trial	Romosozumab (Evenity, AMG-785, CDP-7851), NCT02186171, 20110174 (Amgen), 2013-005551-32 (EudraCT Number); men with osteoporosis; romosozumab vs placebo; Phase III
Sponsor	UCB and Amgen
Status	Completed and published in abstract
Source of Information	Abstract - American College of Rheumatology (ACR) and Association of Rheumatology Health Professionals (ARHP) 2016 Annual Meeting,[4] Adis Insight[3]

	Company[22]
Location	EU (not UK), USA and other countries
Design	Randomised, placebo-controlled, double-blind, parallel, prospective.
Participants	n= 245; male subjects ≥ 55 years to ≤ 90 years of age with osteoporosis defined as a hip or spine BMD T-score ≤ -2.5 or a BMD T-score ≤ -1.5 with a history of fragility fracture.
Schedule	Randomised to subcutaneous injections of romosozumab (210mg) monthly for 12 months; or subcutaneous injections of placebo monthly for 12 months. All subjects received daily calcium and vitamin D.
Follow-up	Active treatment monthly for 12 months. No follow-up period beyond 12 months.
Primary Outcomes	Percent changes from baseline in bone mineral density (BMD) at the lumbar spine at Month 12 as assessed by dual-energy x-ray absorptiometry (DXA)
Secondary Outcomes	Percent changes from baseline in DXA BMD at the femoral neck and total hip at Month 12. Percent changes from baseline in DXA BMD at the lumbar spine, femoral neck, and total hip at Month 6. Percentage changes from baseline in the serum bone turnover markers P1NP and CTX, respectively. Safety endpoints included incidence of adverse events (AEs). No quality of life measurement included in trial outcomes
Key Results	A total of 245 men were enrolled (n=163 romosozumab, n=82 placebo) with a baseline mean (SD) age of 72 (7.3) years. The results demonstrated statistically significant 12% ($p < 0.01$) increase in bone mineral density (BMD) at the lumbar spine in men with osteoporosis treated with romosozumab compared with placebo. Statistically significant increase in BMD was also observed at the femoral neck (2.2%) and total hip (2.5%) at 12 months (both $p < 0.01$ compared to placebo) in comparison with the placebo. At six months, a statistically significant increase in BMD was also achieved with romosozumab at lumbar spine (9.0%), total hip (1.6%), femoral neck (1.2%; $p < 0.01$ for all sites) Romosozumab treatment also resulted in a rapid and transient increase in the bone formation marker P1NP that peaked at

	month 1 (median increase from baseline 86%) and gradually returned toward baseline. The bone resorption marker CTX decreased after the first dose of romosozumab, with the greatest decrease observed at month 1 (median decrease from baseline 31%), and remained below baseline through month 12.
Adverse effects (AEs)	The overall subject incidence rates of AEs and serious AEs were balanced between treatment groups. Injection site reactions were reported in 5.5% and 3.7% of subjects in the romosozumab and placebo groups, respectively; most reactions were reported as mild in severity. The subject incidence of positively adjudicated cardiovascular serious AEs was 4.9% (8/163) in the romosozumab group and 2.5% (2/81) in the placebo group. The subject incidence of positively adjudicated cardiovascular death was 0.6% (1/163) in the romosozumab group and 1.2% (1/81) in the placebo group.
Expected reporting date	-

ESTIMATED COST and IMPACT

COST

The cost of romosomuzab is not yet known.

IMPACT – SPECULATIVE

IMPACT ON PATIENTS AND CARERS

☒ Reduced mortality/increased length of survival

☒ Reduced symptoms or disability

☐ Other:

☐ No impact identified

IMPACT ON HEALTH and SOCIAL CARE SERVICES

☐ Increased use of existing services

☐ Decreased use of existing services

☐ Re-organisation of existing services

☐ Need for new services

☐ Other ☒ None identified

IMPACT ON COSTS and OTHER RESOURCE USE

☐ Increased drug treatment costs ☐ Reduced drug treatment costs

☐ Other increase in costs ☐ Other reduction in costs

☐ Other ☒ None identified

OTHER ISSUES

☐ Clinical uncertainty or other research question identified ☒ None identified

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