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Romosozumab for postmenopausal osteoporosis

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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 in women with postmenopausal osteoporosis has been evaluated in phase II and phase III clinical trials. Two of the three phase III studies have been completed (STRUCTURE and FRAME) and one is still currently ongoing (ARCH). The results of these studies demonstrates that romosozumab works quickly within 12 months to form new bone and lower the risk of a fracture, providing a new treatment strategy for patients with osteoporosis to quickly build bone strength before transitioning to anti-resorptive treatment to maintain the gains.

TARGET GROUP

Postmenopausal women at high risk of fracture.

TECHNOLOGY

DESCRIPTION

Romosozumab (AMG-785; CDP-7851) is a humanized monoclonal antibody under development for the treatment of bone-related conditions, which includes postmenopausal osteoporosis and osteoporosis in males. Romosozumab reduces fragility fracture risk within 12 months and the risk reduction can be maintained after transition to anti-resorptive treatment. The drug originated as a result of a genetic discovery on the body's natural ability to increase bone strength and is a new monoclonal antibody that targets sclerostin, a protein secreted by bone cells that inhibits bone formation. When the sclerostin function is inhibited, bone formation is stimulated and bone resorption is reduced thereby rapidly increasing bone mass, structure and strength.[1]

In one phase III clinical trial, romosozumab was administered through subcutaneous injections (210 mg) monthly for 12 months, followed by subcutaneous open-label denosumab for 24 months in post-menopausal women with osteoporosis.[2] In a second phase III clinical trial, romosozumab was administered through subcutaneous injections (210 mg) monthly for 12 months, followed by subcutaneous open-label alendronate (oral) for at least another 12 months in post-menopausal women with osteoporosis.[3]

A Phase IIIb study was conducted that compared 12 months of romosozumab with 12 months of teriparatide in postmenopausal women with osteoporosis who were previously treated with an oral bisphosphonate and directly transitioned to either romosozumab or teriparatide.[4]

Romosozumab has also been studied in men with osteoporosis in a phase III clinical trial where it was compared with placebo over a 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) at the end of the study period.[3, 4]

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

INNOVATION and/or ADVANTAGES

If licensed, romoszumab is expected to target osteoporosis in postmenopausal women with a high risk of bone fractures in the near term. Most osteoporosis drugs work by stopping the progression of bone loss. Romosozumab is unique in that it stimulates bone formation and also reduces bone resorption. It is a 1 year treatment that rapidly builds bone mass and decreases fracture risk within 12 months and should then be followed by an anti-resorptive treatment to maintain the gains obtained with romosozumab.[5]

DEVELOPER

UCB; Amgen

AVAILABILITY, LAUNCH or MARKETING

It is currently in clinical trials phase III.

PATIENT GROUP

BACKGROUND

Osteoporosis is a condition that weakens bones over time, making them more likely to break. Approximately 1 in 2 women and 1 in 5 men over age 50 will have an osteoporosis-related fracture in their lifetime.[6]

Postmenopausal women with osteoporosis considered 'high risk' are those with a bone mineral density (BMD) that is 2.5 standard deviations (SDs) or more below the young adult mean value for women (T-score equal to or less than –2.5 SD).[7]

Women often are not aware that they have osteoporosis because it does not become clinically apparent until a fracture occurs. When fractures do occur they can cause substantial pain and disability and can be life altering for some patients particularly with hip and vertebral fractures making it harder for patient to remain mobile and do things on their own, rapidly leading to loss of independence. When a fracture occurs this is a sign of weakened bones and inadequate bone strength, and that future fractures are likely, unless treatment is taken to reverse those deficits.[7]

CLINICAL NEED and BURDEN OF DISEASE

Around 3 million women and men have osteoporosis in the UK[8] and an estimated 500,000 fragility fractures occur each year in the UK.[9]

A postmenopausal woman has a 50% risk of sustaining an osteoporosis-related fracture in her lifetime while men over the age of 50 years have a 20% risk. Importantly, following a fracture the risk of subsequent fractures increases substantially.[10]

Once a woman suffers a fragility fracture, she is 5 times more likely to suffer another fracture within just 1 year and many women worry about another fracture and the impact it may have on their life.

In 2010, fragility fractures were estimated to cost £4.3 billion in the UK, a burden expected to increase with a growing ageing population to more than £5.4 billion by 2025. 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.[11] The Royal College of Physicians (RCP) audited the quality of clinical care delivered to patients who had fallen and fractured a bone, and had been seen in a hospital emergency department (A&E).[12] Only 32% of those with a non-hip fracture received adequate fracture risk assessment and just 28% were established on anti-osteoporosis medications within 12 weeks. Of these, the percentages were much lower for those not admitted to hospital. The department of Health (DH) subsequently incentivised primary care to initiate these treatments for such patients but, by the end of the first year of this scheme, fewer than one in five patients were on treatment.[13] Of those treated with oral bisphosphonates, short- and medium-term adherence to anti-osteoporosis medication is less than 50% in primary care.[14]

Commonly used treatments for osteoporosis take longer than 1 year to reduce clinical fracture risk and there is currently only one bone-forming agent available in the UK, requiring daily injections.[9]

The population likely to be eligible to receive romosozumab is still to be confirmed but is expected to include patients who have already experienced a fragility fracture, as these patients are at a higher risk for further fractures, particularly in the 12 – 24 months following the initial fracture.

PATIENT PATHWAY

RELEVANT GUIDANCE

NICE GUIDANCE

- NICE technology appraisal in development. Biphosphonates for preventing osteoporotic fragility fractures (including a partial update of NICE technolgy appraisal guidance 160 and 161) (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 (amended) (TA160). October 2008.
- NICE clinical guideline. Osteoporosis: assessing the risk of fragility fracture (CG146). August 2012. (Updated February 2017).

NHS ENGLAND and POLICY GUIDANCE

- 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.
- NICE Quality Standard 149 Apr 2017. Osteoporosis.

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
  http://www.shef.ac.uk/NOGG/NOGG_Pocket_Guide_for_Healthcare_Professionals.pdf

CURRENT TREATMENT OPTIONS

Postmenopausal osteoporosis may be treated with a bisphosphonate. The bisphosphonates (such as alendronate and risedronate) decrease the risk of vertebral fracture; alendronate and risedronate have also been shown to reduce non-vertebral fractures.[9]

Teriparatide, a form of the hormone which regulates calcium levels in your body (parathyroid hormone) has also been recommended by NICE as a treatment option for postmenopausal osteoporosis.[15] It is administered as a daily subcutaneous injection for 18 to 24 months.[9] Denosumusab, an anti-resorptive treatment, given subcutaneously every 6 months, is a monoclonal antibody used to treat osteoporosis in women after menopause who are at high risk for fracture.[7]

EFFICACY and SAFETY

Trial	Romosozumab (Evenity, AMG-785, CDP-7851), NCT01575834 (FRAME); Postmenopausal osteoporosis; romosozumab vs placebo; phase III	Romosozumab (Evenity, AMG-785, CDP-7851), NCT01631214 (ARCH); Postmenopausal osteoporosis; Romosozumab vs alendronate; phase III	Romosozumab (Evenity, AMG-785, CDP-7851), NCT01796301 (STRUCTURE); Postmenopausal osteoporosis; Romosozumab vs teriparatide; phase III	Romosozumab (Evenity, AMG-785, CDP-7851), NCT00896532, Postmenopausal Women with Low Bone Mineral Density; AMG 785 or placebo or debomusab vs open label teriparatide or alendronate or zolendronic acid; phase II
Sponsor	UCB, Amgen	UCB; Amgen	UCB; Amgen	UCB; Amgen
Status	Primary analysis reported, extension is ongoing	Ongoing, but not recruiting participants	Completed	Completed
Source of Information	Trial registry[2]	Trial registry[3]	Trial registry[4]	Trial Registry[16]
Location	EU (Including UK), North America, South America, Asia	EU (Including UK), North America, South America, Asia	EU (Including UK), North America, South America	Argentina, EU(non UK) and USA
Design	Randomised, double blind controlled	Randomised and double blind controlled.	Randomised, open label controlled	Randomised and placebo controlled.
Participants	N = 7180; aged 55 to 90 years; females; Postmenopausal with osteoporosis defined as low bone mineral density.	N=4093; aged 55 to 90 years; females; Postmenopausal with osteoporosis at high risk of fracture defined as: a hip BMD T-score ≤ -2.50 and a vertebral fracture or a hip BMD T-score ≤ 2.00 and a	n = 436; aged ≥ 55 to ≤ 90; postmenopausal women with a BMDT-score of ≤ -2.5 at the femoral neck, spine or hip, a history of fragility fracture and that had received oral bisphosphonate therapy for	N=419; aged 55 to 85 years; females; Postmenopausal with osteoporosis.

		recent hip fracture or two vertebral fractures.	at least 3 years immediately prior to screening.	
Schedule	Romosozumab sub-cutaneous injections for 12 months, followed by sub-cutaneous open-label denosumab injections for another 12 months Sub-cutaneous placebo injections for 12 months, followed by sub-cutaneous open-label denosumab injections for another 12 months	Romosozumab sub-cutaneous injections for 12 months followed by open-label alendronate (oral) for at least another 12 months (until end of study). Oral alendronate for 12 months, followed by open-label alendronate, (oral) for at least another 12 months (until end of study)	Romosozumab subcutaneous injections for 12 months Teriparatide for 12 months	Drug: Active Comparator Alendronate 70mg PO every week (QW) • Placebo- SC Q3M • AMG 785 :140mg SC QM • AMG 785 :140mg SC Q3M • AMG 785 :210mg SC Q3M • Placebo :SC QM • Active comparator teriparatide 20µg SC every day (QD) • AMG 785 :210mg SC QM • AMG 785 :70mg SC QM • Denosumab :60 mg SC Q6M • Zoledronic acid :5 mg IV • Placebo SC administration every 6 months (Q6M)
Follow-up	After 24 months patients enter an extension phase for another 12 months	Active treatment period for up to 36 months.	No-follow-up period beyond 12 months	Active treatment period for up to 12 to 72 months, follow-up period 12 months.
Primary Outcomes	Incidence of new vertebral fracture at 12 and 24 months	Incidence of clinical fracture; Incidence of new vertebral fracture	Percent changes in total hip DXA BMD through 12 months	Percent change from baseline at month 12 in bone mineral density at the lumbar spine for the individual AMG 785 groups and pooled placebo arms
Secondary Outcomes	Incidence of fractures Percent changes in DXA bone mineral density (BMD)	Incidence of fractures	Total hip BMD at 6 months Femoral neck and lumbar	Percent change from baseline at month 12 in bone mineral density at the total hip,

	at the lumbar spine, total hip, and femoral neck at 12 and 24 months	Percent changes in DXA Bone Mineral Density from baseline to 12 months; Percent changes in DXA Bone Mineral Density from baseline to 24 months; Percent changes in DXA Bone Mineral Density from baseline to 36 months	spine DXA BMD at 6 and 12 months	femoral neck and distal radius for the individual AMG 785 groups and pooled placebo arms. Percent change from baseline at month 1, 3, 6, 9 and 12 in bone turnover markers for the individual AMG 785 groups and pooled placebo arms. Nature, frequency, severity of adverse events & their relationship to treatment; Changes from baseline in vital signs, laboratory assessments, ECG parameters; Bone histologic & histomorphometric pameters; Formation of anti-AMG 785 antibodies. Percent change from baseline at month 24 in bone mineral density for the individual AMG 785 groups and pooled placebo arms. Percent change from baseline in Quantitative Computed Tomography (QCT) BMD & variables for AMG 785 and teriparatide groups during the first year.Percent change from baseline at month 6 in bone mineral density at the lumbar spine, total hip and femoral neck for the individual AMG

				785 groups and pooled placebo arms Nature, frequency and severity of adverse events and their relationship to treatment; Percent change from baseline and month 48 to months 54, 60, 66, and 72 in BMD at the lumbar spine, total hip, and femoral neck. Percent change from baseline and month 48 to months 51, 54, 60, 66, and 72 in BTMs.
Key Results	At 12 months romosozumab demonstrated a significant 73% relative risk reduction in new vertebral fractures versus placebo. At 12 months romosozumab demonstrated a significant 36% relative risk reduction in clinical fracture versus placebo. At 12 months romosozumab led to a non-statistically significant 25% relative risk reduction in nonvertebral fractures (P=0.10). Significant treatment-by-region interactions were	-	BMD at all sites significantly improved through month 12 with romosozumab compared to teriparatide.	All dose levels of romosozumab were associated with significant increases in bone mineral density at the lumbar spine. It was also associated with large increases in bone mineral density at the hip and femoral neck, as well as transitory increases in bone-formation markers and sustained decreases in a bone-resorption marker.

	observed for clinical and nonvertebral fractures across geographic regions. In a post-hoc analysis, the incidence of nonvertebral fracture in the region of Latin America was very low in the placebo group (1.2%) and was not reduced in the romosozumab group (1.5%). By contrast, among the patients outside the region of Latin America, the incidence was 2.7% in the placebo group and significantly reduced to 1.6% in the romosozumab group, representing a risk that was 42% lower in the romosozumab group (hazard ratio, 0.58, 95% CI, 0.37 to 0.89; P=0.04 for the treatment-by-region interaction). At 24 months romosozumab demonstrated a significant 75% relative risk reduction in new vertebral fracture versus the placebo group after each group made the transition to denosumab.			

	At 24 months, a 33% relative risk reduction in clinical fractures was observed in the romosozumab group versus the placebo group after each group made the transition to denosumab. At 24 months, the romosozumab group demonstrated a 25% relative risk reduction in non-vertebral fractures versus the placebo group after each group made the transition to denosumab.			
Adverse effects (AEs)	The incidence of adverse events and serious adverse events was balanced in the two arms, as was the incidence of events that were categorised as osteoarthritis, hyperostosis, cancer, hypersensitivity, and adjudicated serious cardiovascular events. Two events that occurred in patients in the romosozumab group were adjudicated as being consistent with the	-	The overall incidence of adverse events was generally balanced between the two study arms. Incidence of all adverse events in patients treated with romosozumab was 75.2 percent compared to 69.2 percent with teriparatide. Serious adverse events occurred in 7.8 percent of patients treated with romosozumab compared to 10.7 percent for teriparatide.	Except for mild, generally nonrecurring injection-site reactions with romosozumab, adverse events were similar among groups

	definition of osteonecrosis of the jaw. One event occurred after 12 months of romosozumab treatment in the context of ill-fitting dentures, and the other event occurred after 12 months of romosozumab treatment and one dose of denosumab after a tooth extraction and subsequent osteomyelitis of the jaw. One event that was adjudicated as being consistent with the definition of atypical femoral fracture occurred 3.5 months after the first dose of romosozumab; the patient had reported a history of prodromal pain at the site of fracture beginning before enrolment.			
Expected reporting date	Reported	Expected 2017	Reported	Study completion date reported as Jan 2014

ESTIMATED COST and IMPACT

COST

The cost of romosomuzab is not yet known.

Drug	Dose	Annual cost*
Alendronate	10mg once daily 70mg oral, once weekly	£21.12 £9.36
Teraparatide	20µg SC, once daily	£3,544.15
Denosumab	60mg SC, every 6 months	£366.00

*British National Formulary. BNF 2017. www.bnf.org

IMPACT – SPECULATIVE

IMPACT ON PATIENTS and CARERS

☐ Reduced mortality/increased length of survival

☒ Reduced symptoms or disability

☒ *potential improvement in quality of life for carers improved patient convenience, wider societal benefits (e.g. earlier return to normal activities, including employment)*

☐ 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: *unknown cost of new therapy* ☐ None identified

OTHER ISSUES

☐ Clinical uncertainty or other research question identified: *specify* ☒ None identified

REFERENCES

1 Amgen. Results From Phase 3 FRAME Study Of Romosozumab Showed Significant Reductions In Both New Vertebral And Clinical Fractures In Postmenopausal Women With Osteoporosis. 2016.

2 ClinicalTrials.gov. Efficacy and Safety of Romosozumab Treatment in Postmenopausal Women With Osteoporosis (FRAME). 2017 [cited 2017 10 May]; Available from: https://clinicaltrials.gov/ct2/show/NCT01575834

3 ClinicalTrials.gov. Study to Determine the Efficacy and Safety of Romosozumab in the Treatment of Postmenopausal Women With Osteoporosis. 2017.

4 ClinicalTrials.gov. An Open-label Study to Evaluate the Effect of Treatment With AMG 785 or Teriparatide in Postmenopausal Women (STRUCTURE) (STRUCTURE). 2016 [cited 2017 10 May]; Available from: https://clinicaltrials.gov/ct2/show/NCT01796301

5 Amgen. Amgen And UCB Announce U.S. FDA Acceptance Of Biologics License Application For Romosozumab. 2016.

6 Cosman F, Crittenden DB, Adachi JD, Binkley N, Czerwinski E, Ferrari S, et al. Romosozumab Treatment in Postmenopausal Women with Osteoporosis. New England Journal of Medicine. 2016;375(16):1532-43.

7 Prolia. What Is Postmenopausal Osteoporosis? . 2017.

8 Ivergard Mea. Epidemiology and Economic Burden of Osteoporosis in the UK. Arch Osteoporosis. 2013;8(13).

9 Escellence NIfHaC. Osteoporosis: assessing the risk of fragility fracture Clinical guideline [CG146]. 2017 [cited 2017 10 May]; Available from: https://www.nice.org.uk/guidance/cg146

10 Gauthier A, Kanis JA, Jiang Y, Martin M, Compston JE, Borgström F, et al. Epidemiological burden of postmenopausal osteoporosis in the UK from 2010 to 2021: estimations from a disease model. Archives of Osteoporosis. 2011;6(1):179-88.

11 UK ILC. Osteoporosis in the UK at breaking point. . 2010.

12 Physicians RCo. Falling standards, broken promises: report of the national audit of falls and bone health. 2013 [cited 2017 10 May]; Available from: https://www.rcplondon.ac.uk/projects/outputs/falling-standards-broken-promises-report-national-audit-falls-and-bone-health

13 Centre HSCI. Quality and Outcomes Framework Achievement, prevalence and exceptions data, 2012/13. 2013 [cited 2017 10 May]; Available from: http://content.digital.nhs.uk/catalogue/PUB12262/qual-outc-fram-tech-anne-2012-13-anx.pdf

14 Li L, Roddam A, Gitlin M, Taylor A, Shepherd S, Shearer A, et al. Persistence with osteoporosis medications among postmenopausal women in the UK General Practice Research Database. Menopause. 2012;19(1):33-40.

15 Excellence NIfHaC. Osteoporosis: assessing the risk of fragility fracture Clinical guideline [CG146]. 2012.
16 ClinicalTrials.gov. Phase 2 Study of AMG 785 in Postmenopausal Women With Low Bone Mineral Density 2017 [cited 2017 17/05]; Available from: https://clinicaltrials.gov/show/NCT00896532