SIGN
Scottish Intercollegiate Guidelines Network

Management of osteoporosis and prevention of fragility fractures

SIGN 142 Update 2020

Stuart H Ralston MD, FRCP, FMedSci, FRSE
Professor of Rheumatology

Healthcare Improvement Scotland

SIGN 142

Management of osteoporosis and the prevention of fragility fractures

A national clinical guideline

First published March 2015
Revised edition published June 2020

Need for an update

- New evidence on risk factors
- New data on existing treatments
- Development of a new treatment
- Some treatments withdrawn

The SIGN update team

Professor Stuart Ralston, Rheumatologist, Edinburgh,
Dr Jamie Fraser, GP, Inverness
Dr Stephen Gallacher, Endocrinologist, Glasgow
Professor Philip Hannaford Epidemiologist Aberdeen
Dr Rosemary Hollick, Rheumatologist, Aberdeen
Dr Jenni Hislop, Health Economist, Healthcare Improvement Scotland
Mrs Catherine McConnell, Patient Representative, Glasgow
Mrs Gill Pullan, Patient representative, Nairn
Ms Naomi Scott, Pharmacist, NHS Lothian
Ms Lynne Smith, Information Scientist, Healthcare Improvement Scotland
Dr Rajeev Srivastava, Consultant Chemical Pathologist, Glasgow
Ms Ailsa Stein Programme Manager, SIGN
Ms Margaret Yates, Osteoporosis Specialist Nurse, Lanarkshire

SIGN 142 update process and timeline

- Previous guideline published 2015
- Need for update discussed 2017
- Topics requiring update identified 2017-2018
- Update agreed by SIGN board June 2018
- Guideline development meetings 2018-2019
- Covid19
- Final Guidance published June 2020

Main areas of update

- **Risk factors**
  - HIV infection
- **Targeting treatment**
  - Role of population-based screening
- **Old treatments removed**
- **New data on existing treatments**
  - Teriparatide
  - Zoledronic acid
  - Denosumab
- **New treatments**
  - Romosozumab

Risk factors

- **SIGN 142 Original**
  - *Insufficient evidence to determine whether HIV infection predisposes to osteoporosis and fractures independent of treatments and other risk factors*
- **SIGN 142 Update**
  - *People living with human immunodeficiency virus should be considered as being at increased risk of fracture (at any site) and should be considered for fracture risk assessment, particularly where other risk factors are present*

Targeting treatment by population-based screening

Osteoporosis International (2018) 29:567–578
https://doi.org/10.1007/s00198-017-4326-3

ORIGINAL ARTICLE

Effectiveness of a two-step population-based osteoporosis screening program using FRAX: the randomized Risk-stratified Osteoporosis Strategy Evaluation (ROSE) study

K. H. Rubin[1] · M. J. Rothmann[2,3] · T. Holmberg[4] · M. Høiberg[3,5] · S. Möller[1] · R. Barkmann[6] · C. C. Glüer[6] · A. P. Hermann[2,3] · M. Bech[7] · J. Gram[3,8] · K. Brixen[3]

Screening in the community to reduce fractures in older women (SCOOP): a randomised controlled trial

*Lee Shepstone, Elizabeth Lenaghan, Cyrus Cooper, Shane Clarke, Rebekah Fong-Soe-Khioe, Richard Fordham, Neil Gittoes, Ian Harvey, Nick Harvey, Alison Heawood, Richard Holland, Amanda Howe, John Kanis, Tarnya Marshall, Terence O'Neill, Tim Peters, Niamh Redmond, David Torgerson, David Turner, Eugene McCloskey; for the SCOOP Study Team**

Summary

Background Despite effective assessment methods and medications targeting osteoporosis and related fractures, screening for fracture risk is not currently advocated in the UK. We tested whether a community-based screening intervention could reduce fractures in older women.

Lancet 2018; 391: 741–47
Published Online
December 15, 2017

Targeting treatment by population-based screening

- SCOOP study
  - Women aged 70-85 (n=12,483)
  - FRAX based screening followed by DEXA in high risk group with recalculation of fracture risk
  - High-risk group offered treatment (average T-score -2.6)
  - Osteoporosis medication use higher in screened group
  - No overall reduction of fractures in screened group
    - 0.94 (0.86-1.03)
  - Hip fractures reduced in screened group
    - 0.72 (0.59-0.89)

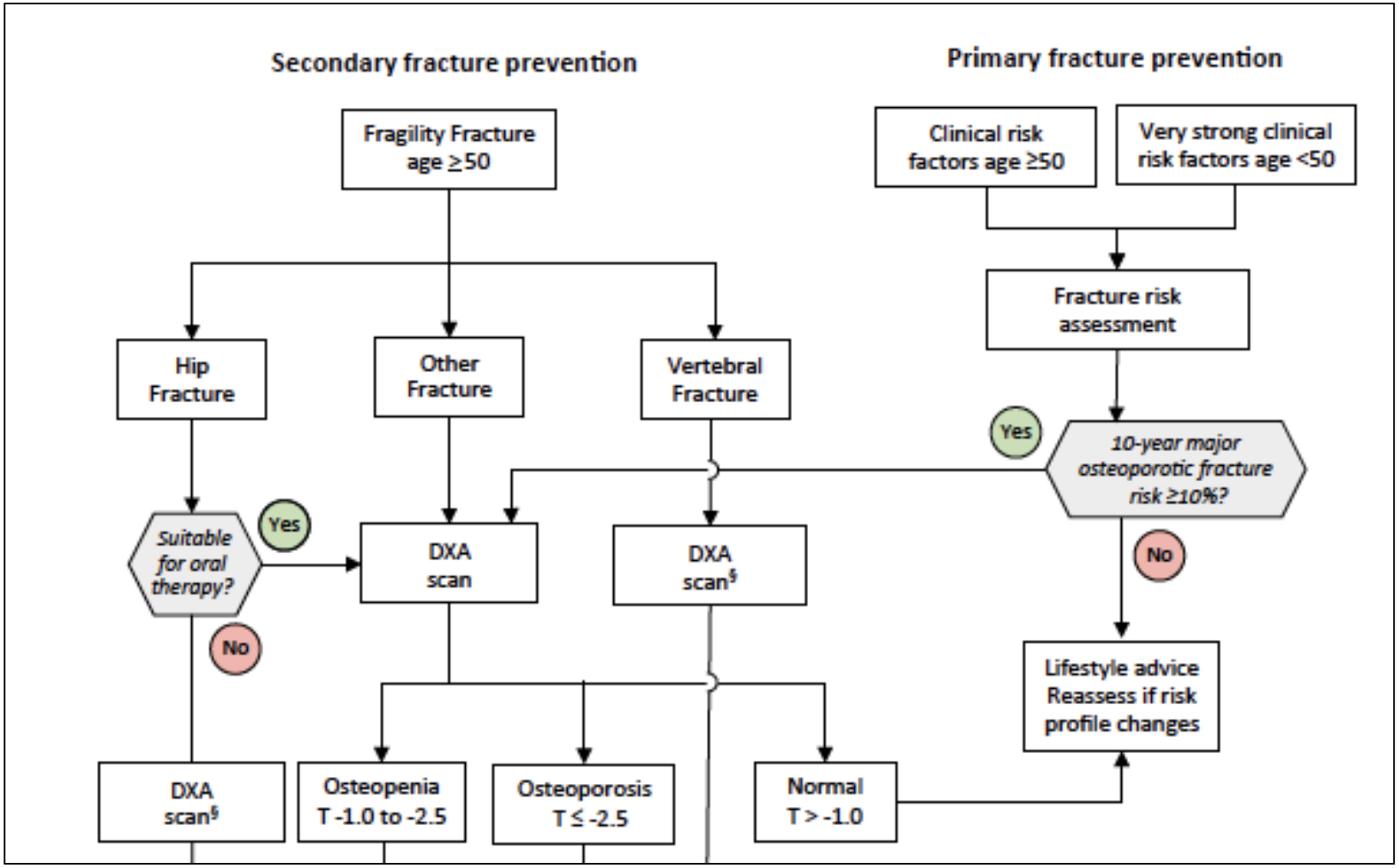
Targeting treatment by population-based screening

- ROSE study
  - FRAX based screening followed by DEXA
  - Offer of treatment in high risk group with DEXA proven osteoporosis (as per clinical guidance in Denmark)
  - No overall reduction in fractures in screened group.
    - All fractures = 1.04 [0.94-1.06]
  - Subjects who underwent screening and had DEXA showed reduced fractures
    - All fractures = 0.87 [0.78-0.97]
    - Hip fractures = 0.70 [0.55-0.91]

SIGN advice on population- based screening

- **SIGN 142**
  - *Population-based screening for fracture risk coupled with an offer of treatment of those at high risk of fracture is not recommended as a means of reducing major osteoporotic fractures*
- **Conclusions of SIGN in keeping with those of UK National Screening Committee**

Algorithm for detecting osteoporosis



Management of osteoporosis

- New data on Teriparatide
  - VERO study (teriparatide versus risedronate)
  - Oswald study (teriparatide versus standard care)
- New data on Zoledronic acid
  - Efficacy in osteopenic women
- New data on safety of denosumab
  - Vertebral fracture risk on discontinuation
- New treatment licensed
  - Romosozumab
- Recommendations for etidronate removed
- Vitamin K not recommended

Role of teriparatide in osteoporosis

Effects of teriparatide and risedronate on new fractures in post-menopausal women with severe osteoporosis (VERO): a multicentre, double-blind, double-dummy, randomised controlled trial

David L Kendler, Fernando Marin, Cristiano A F Zerbini, Luis A Russo, Susan L Greenspan, Vit Zikan, Alicia Bagur, Jorge Malouf-Sierra, Péter Lakatos, Astrid Fahrleitner-Pammer, Eric Lespessailles, Salvatore Minisola, Jean Jacques Body, Piet Geusens, Rüdiger Möricke, Pedro López-Romero

Calcified Tissue International (2019) 105:148–155
https://doi.org/10.1007/s00223-019-00563-8

ORIGINAL RESEARCH

Long-Term Effects of Teriparatide Followed by Antiresorptive Therapy on Clinical Outcomes in Patients with Severe Spinal Osteoporosis

Ailsa J. Oswald[1] · Kathryn Berg[1] · Stuart H. Ralston[1] · Philip L. Riches[1]

Received: 13 February 2019 / Accepted: 6 May 2019 / Published online: 21 May 2019

Role of teriparatide in osteoporosis

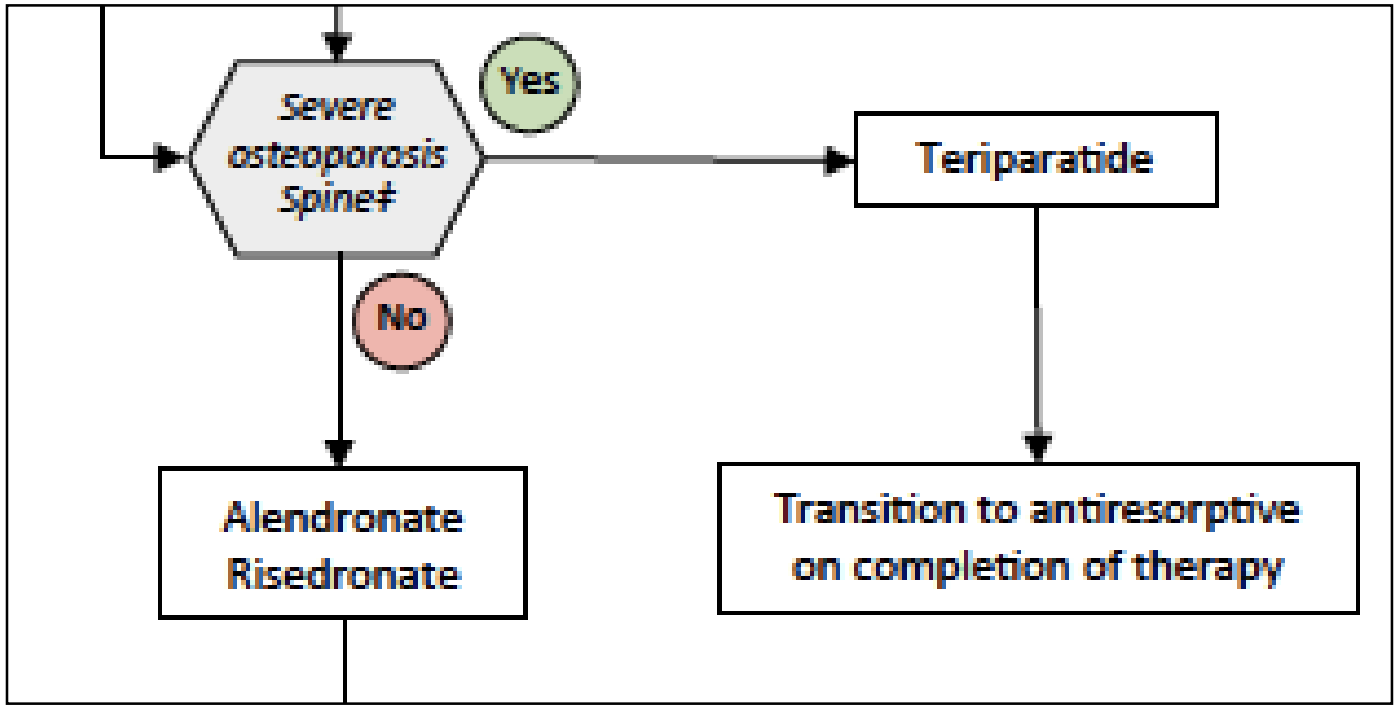
- **VERO study**
  - 1360 postmenopausal women with vertebral fractures
  - Treated with TPTD or RIS for 2 years
  - Fewer new vertebral fractures with TPTD (5.4% vs 12.0%)
  - No difference in non-vertebral fractures
- **Oswald study**
  - Observational study of 724 women with severe spinal osteoporosis offered TPTD followed by antiresorptive or standard care
  - Fewer new spine fractures in TPTD group after adjustment for confounders (4.8% vs 10.1%)
  - No difference in non vertebral fractures.

SIGN advice on Teriparatide

Section 6.4.8

- *Teriparatide is recommended to prevent vertebral and non-vertebral fractures in postmenopausal women with severe osteoporosis*
- *In post menopausal women with at least two moderate or one severe low trauma vertebral fractures, teriparatide is recommended over oral bisphosphonates, for vertebral fracture risk reduction.*
- *As teriparatide discontinuation is associated with bone loss, treatment with an antiresorptive agent may be considered to maintain the increase in bone density once the course of TPTD has been completed.*

Role of TPTD in SIGN 142 algorithm



Severe osteoporosis spine: T-score <-1.5 and two or more grade 2 vertebral fractures or spine T-score <-4.0

Zoledronic acid in osteopenia

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Fracture Prevention with Zoledronate in Older Women with Osteopenia

Ian R. Reid, M.D., Anne M. Horne, M.B., Ch.B., Borislav Mihov, B.Phty., Angela Stewart, R.N., Elizabeth Garratt, B.Nurs., Sumwai Wong, B.Sc., Katy R. Wiessing, B.Sc., Mark J. Bolland, Ph.D., Sonja Bastin, M.B., Ch.B., and Gregory D. Gamble, M.Sc.

ABSTRACT

Zoledronic acid in osteopenia study

- Postmenopausal women with osteopenia randomised to Zoledronic acid or placebo every 18 months for 6 years
- Average age 71 years, T-score -1.6 and 10-year risk of fracture 12%
- All fragility fractures reduced
  - Odds ratio = 0.63 [0.50-0.79]
- Non-vertebral fractures reduced
  - Odds ratio = 0.66 [0.51-0.85]
- Vertebral fractures reduced
  - Odds ratio = 0.45 [0.27-0.73]

Updated SIGN advice on Zoledronic acid

Section 6.4.3

- *Zoledronic acid may be considered to reduce risk of clinical fractures in women over 65 years of age who have osteopenia at hip or femoral neck on DXA.*
- *The licensed regimen for zoledronic acid is annual 5 mg infusions, but infusions of the same dose every 18 months (off label) for six years are effective at reducing fracture risk.*

Safety of denosumab in osteoporosis

Severe Rebound-Associated Vertebral Fractures After Denosumab Discontinuation: 9 Clinical Cases Report

Olivier Lamy, Elena Gonzalez-Rodriguez, Delphine
and Bérengère Aubry-Rozier

Bone Unit, Lausanne University Hospital, 1011 Lausanne, Swit

Hypercalcemia after discontinuation of long-term denosumab treatment

A. S. Kolthoff Solling[1,2] · T. Harslof[1] · A. Kaal[3] · L. Rejnmark[1] · B. Langdahl[1]

Multiple clinical vertebral fractures following denosumab discontinuation

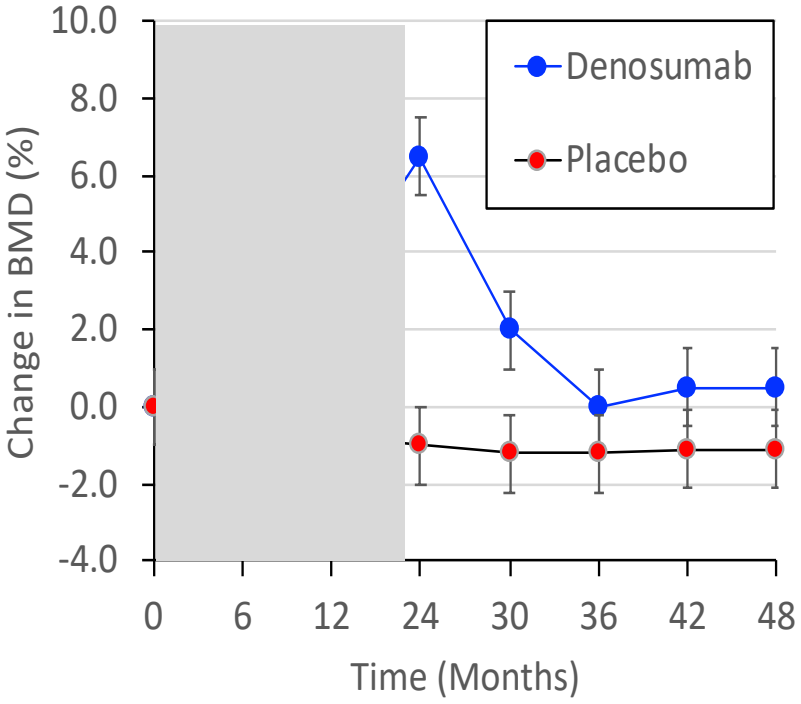
Review Article

Discontinuation of Denosumab therapy for osteoporosis: A systematic review and position statement by ECTS

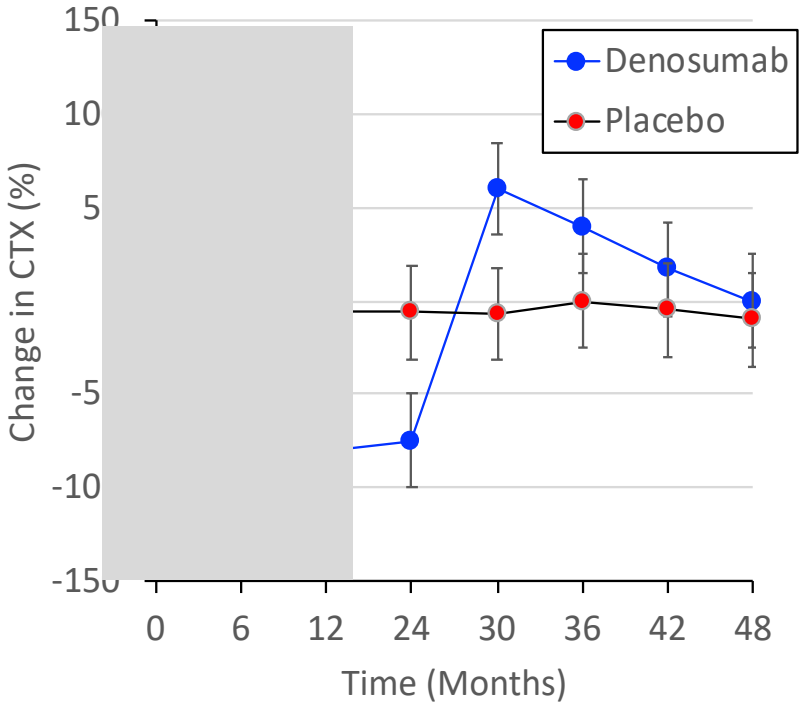
Elena Tsourdi [a,b], Bente Langdahl [c], Martine Cohen-Solal [d], Bérengere Aubry-Rozier [e], Erik Fink Eriksen [f], Nuria Guañabens [g], Barbara Obermayer-Pietsch [h,i], Stuart H. Ralston [j], Richard Eastell [k], M. Carola Zillikens [l,*]

Safety of denosumab in osteoporosis

Spine BMD



CTX



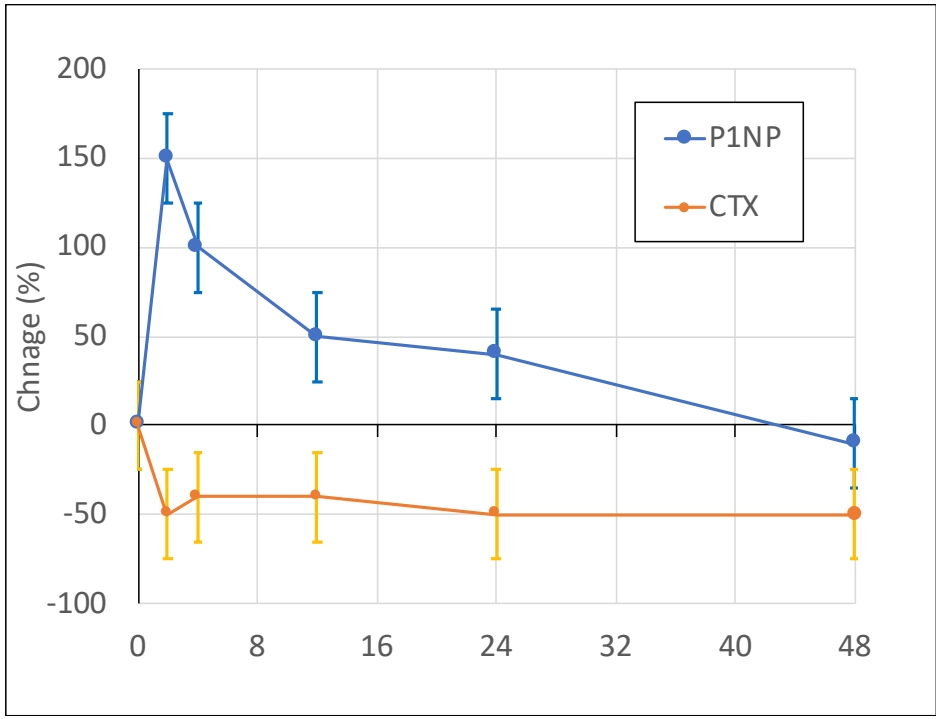
Updated SIGN advice on denosumab

Section 6.4.7

- *Following discontinuation of denosumab, antiresorptive therapy should be considered to ameliorate the rebound increase in bone turnover*

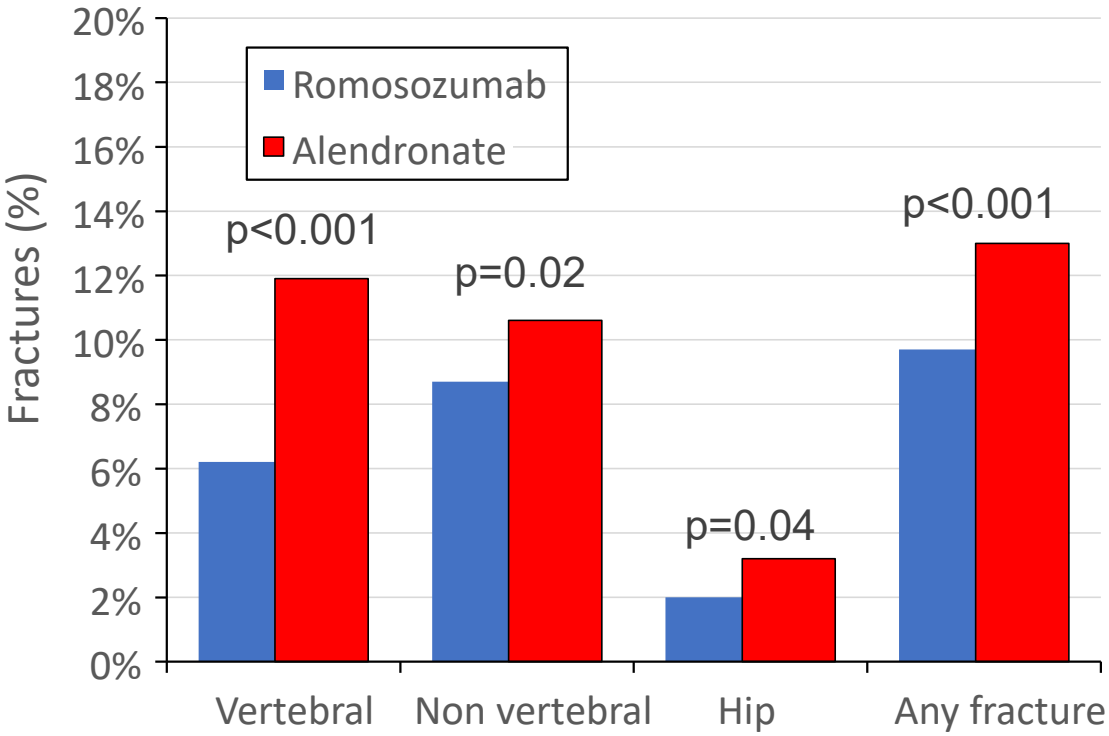
- *Physicians who prescribe denosumab should carefully track the dates when a patient's denosumab is due. It is important to ensure that treatment is given on time (within one month of the scheduled date).*

Romosozumab is an anabolic drug with a unique mechanism of action



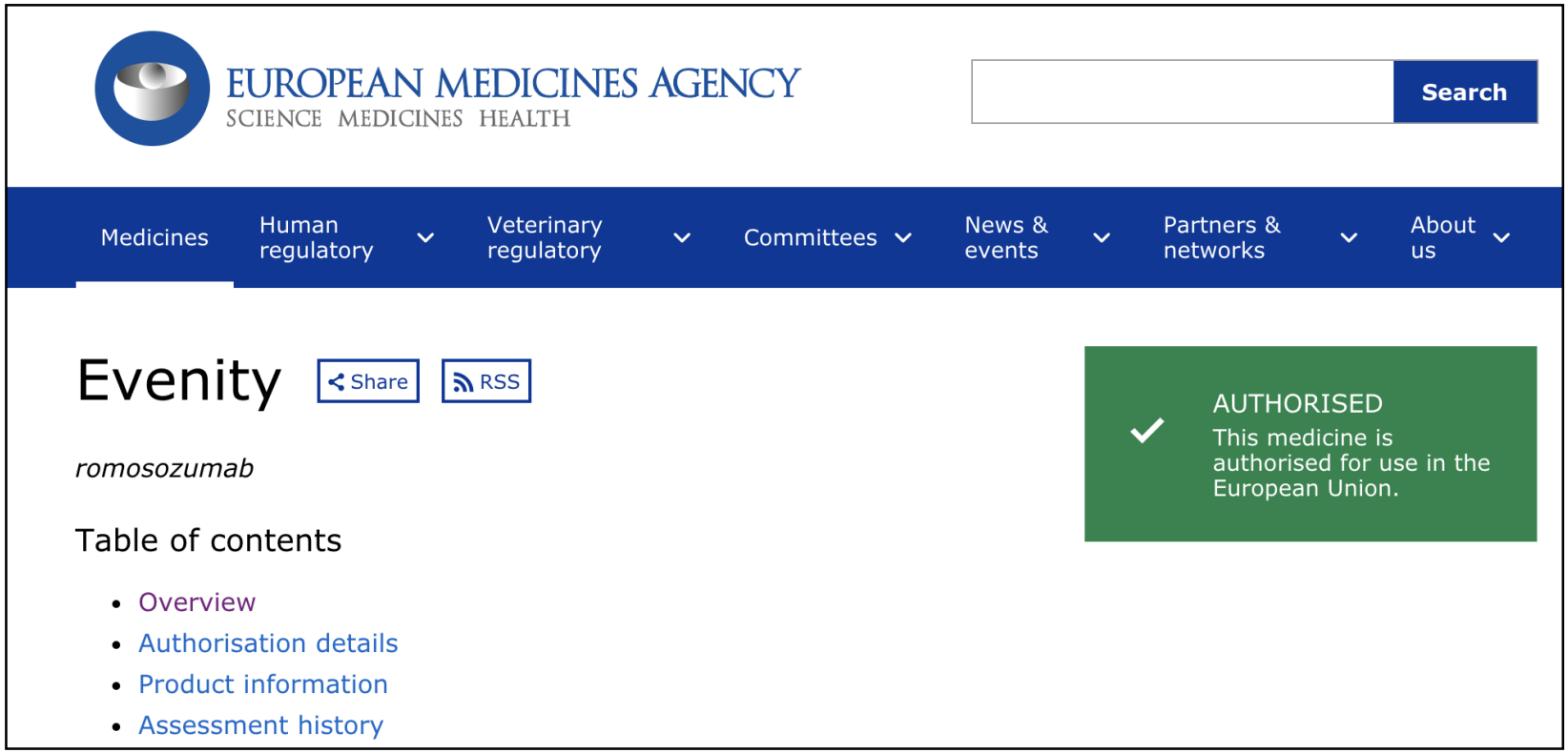
- Mab to sclerostin
- Stimulates bone formation
- Inhibits bone resorption
- Powerful anabolic effect
  - 13.6% increase in spine BMD
  - 6.8% increased in total hip BMD

Romosozumab is superior to alendronic acid in osteoporosis



- **Impressive results but we could not make recommendation as drug not yet considered by SMC**
- **Watch this space!**

Romosozumab approved by the EMA



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Search

Medicines | Human regulatory | Veterinary regulatory | Committees | News & events | Partners & networks | About us

Evenity

Share RSS

romosozumab

AUTHORISED
This medicine is authorised for use in the European Union.

Table of contents

- Overview
- Authorisation details
- Product information
- Assessment history

What did SIGN make of romosozumab?

Section 6.4.9

– *Romosozumab has gained marketing authorisation within the UK and Europe. A decision from the SMC on its use in NHS Scotland is awaited before a recommendation can be made.*

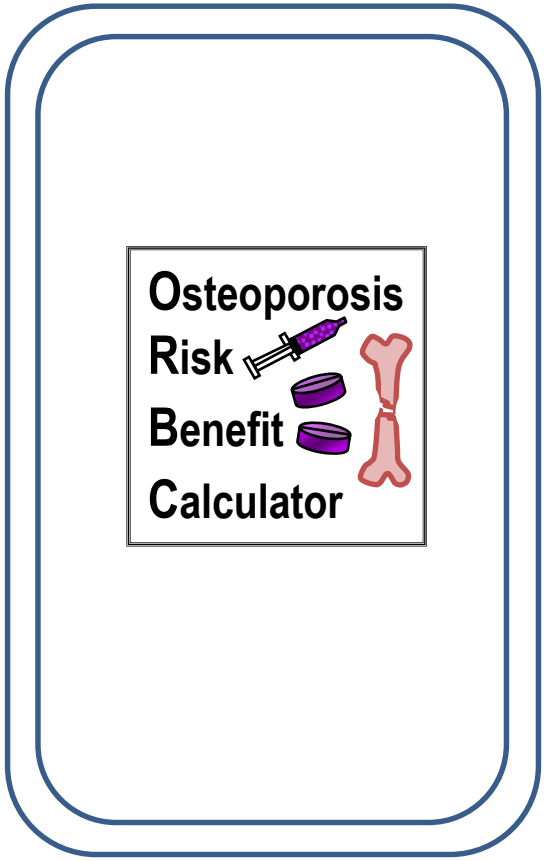
SMC status

– *Submission has been made, and is under review with likely decision in October 2020*

Importance of the patient perspective

Section 1.3.

– *The ultimate judgement must be made by the appropriate healthcare professional(s) responsible for clinical decisions regarding a particular clinical procedure or treatment plan. This judgement should only be arrived at following discussion of the options with the patient, covering the diagnostic and treatment choices available.*



Implications of SIGN update

- Teriparatide may be used more often in severe spinal osteoporosis
- Zoledronic acid now an option in osteopenia
- Take great care when starting and stopping denosumab
- Romosozumab might be a new option for severe osteoporosis