ISRCTN96920058 https://doi.org/10.1186/ISRCTN96920058

DISKO: Effect of denosumab on pain and bone marrow lesions in knee osteoarthritis

Submission date
31/05/2017

Recruitment status
No longer recruiting

Registration date
01/06/2017

Overall study status
Completed

Last Edited
22/08/2022

Condition category
Musculoskeletal Diseases

[X] Prospectively registered
[X] Protocol
[_] Statistical analysis plan
[X] Results
[_] Individual participant data

Plain English summary of protocol

Background and study aims
Knee osteoarthritis (OA) occurs when the protective cartilage on the end of bones wears away. The bones in the knee then rub against one another, causing stiffness, pain and a reduction in the range of movement. Knee OA is the most common cause of knee pain in older adults. Despite this, there are no effective treatments which reduce knee pain and the rate at which the disease progresses. Current treatments are limited due to their side effects and the fact that many are not particularly effective. Recent research, however, suggests that treatments which prevent bone loss may be effective at reducing pain and joint damage in people with knee osteoarthritis. Denosumab is a medication that is used to prevent bone loss and could be helpful to relieve pain for those with knee OA. The aim of this study is to determine whether a one off administration of denosumab, and given as an injection under the skin, is effective at relieving pain in people with painful knee OA and reducing structural damage at the knee.

Who can participate?
Adults aged 50 years and older who have osteoarthritis of the knee

What does the study involve?
Participants undergo an x-ray, blood test and MRI prior to joining the study. They are then randomly allocated to one of two groups. Those in the first group receive a single injection (under the skin) of 60 mg of denosumab. Those in the second group receive a placebo (dummy) injection. Both groups receive a questionnaire to assess their pain and arthritis symptoms. They are instructed to take calcium and vitamin D supplements. Participants attend a follow up appointment three and six months after they receive the injection. One week before each follow up appointment they are asked to wear an activity monitor for seven days. At the three month appointment, participants repeat the questionnaires and undergo a blood test to evaluate their calcium levels. At the six month follow up appointment, participants receive another MRI to assess the changes in their bone marrow lesions and repeat the questionnaire again to see if there has been changes in their knee OA symptoms and pain levels.

What are the possible benefits and risks of participating?
There are no direct benefits with participating. Denosumab has been widely used by physicians for over five years, however, as with any medication there are always potential risks which

should be reviewed with the study doctor or GP. There is a small risk of radiation exposure associated with X-Ray's. Participants may experience claustrophobia (anxiety when in tight spaces) or feel uncomfortable while undergoing the MRI scan. There is a risk of discomfort when providing blood tests.

Where is the study run from?
Salford Royal Hospital (UK)

When is the study starting and how long is it expected to run for?
January 2016 to October 2020

Who is funding the study?
Arthritis UK (UK)

Who is the main contact?
Dr Gillian Armitt
gillian.armitt@manchester.ac.uk

Study website
http://www.manchester.ac.uk/roam

Contact information

Type(s)
Public

Contact name
Dr Gillian Armitt

Contact details
Research in OsteoArthritis Manchester (ROAM)
Centre for Musculoskeletal Research
Division of Musculoskeletal & Dermatological Sciences
School of Biological Sciences
Faculty of Biology, Medicine and Health
The University of Manchester
Stopford Building
Oxford Road
Manchester
United Kingdom
M13 9PT
+44 (0)161 306 0545/0547
gillian.armitt@manchester.ac.uk

Additional identifiers

EudraCT/CTIS number
2016-000754-35

IRAS number

191262

ClinicalTrials.gov number

Secondary identifying numbers
CPMS 34642, IRAS 191262

Study information

Scientific Title
The effect of Denosumab on pain and bone marrow lesions In Symptomatic Knee Osteoarthritis: a randomised double blind placebo controlled clinical trial

Acronym
DISKO

Study objectives
The aim of this study is to determine whether a one off administration of a drug treatment which prevents bone loss called ‘denosumab’, and given as an injection under the skin, is effective at relieving pain in people with painful knee OA and reducing structural damage at the knee.

Ethics approval required
Old ethics approval format

Ethics approval(s)
North West - Greater Manchester South Research Ethics Committee, 22/05/2017, ref: 17/NW /0262

Study design
Randomised; Interventional; Design type: Treatment, Drug

Primary study design
Interventional

Secondary study design
Randomised parallel trial

Study setting(s)
Hospital

Study type(s)
Treatment

Participant information sheet
No participant information sheet available

Health condition(s) or problem(s) studied
Osteoarthritis of the knee

Interventions
Prior to the study, potential participants are screened for eligibility with a knee x-ray, blood test, and a MRI scan to assess for Bone Marrow Lesions (BML). Those who meet the eligibility criteria, including the presence of BML on MRI are accepted to the study. Participants are randomised (50:50) to receiving either a single injection (under the skin) of 60 mg denosumab or to have a matched placebo and fill a questionnaire about their osteoarthritis. Participants receive calcium and vitamin D supplements.

Participants have two follow up appointments three and six months after the initial injection. One week before each appointment participants are also be asked to wear an activity monitor for seven days. At the three month follow up participants repeat the questionnaires to assess their pain and arthritis symptoms as well as undergo a blood test to evaluate their calcium levels. At the six month follow up participants have another MRI scan to assess their change in bone marrow lesions and they also repeating the questionnaire.

Intervention Type
Other

Phase
Phase II

Primary outcome measure
Total area of bone marrow lesions (assessed on MRI) at six months.

Secondary outcome measures
1. Knee pain using an 11 point (0–10) numerical rating scale (NRS) of knee pain intensity, at baseline, three, and six months. The change in knee pain using a NRS scale is the primary outcome recommended by IMMPACT (http://immpact.org/)
2. Knee pain on nominated activity using an 11 point (0-10) numerical rating scale (NRSNA) at three and six months
3. Knee symptoms assessed using KOOS at three and six months
4. Quality of life assessed using EuroQOL & SF12 at three and six months
5. Adverse events are assessed from data collected at each study visit
6. Bone marrow lesions (BML) volume measured on MRI at baseline and six months

Overall study start date
04/01/2016

Completion date
30/10/2020

Eligibility

Key inclusion criteria
Current participant inclusion criteria as of 02/10/2019:
1. Age 40 years and over.
2. Ambulatory (not wheel chair bound), and able and willing to comply with the intervention and follow up.
3. Significant knee pain (have at least a score of 3 out of 10 on the primary symptom outcome of the trial, knee pain on a numerical rating scale (NRS Last week ≥3)

4. Evidence of significant OA on, x-ray – Kellgren Lawrence grade 2 or 3. Participants can have Kellgren and Lawrence grade 2 or 3 in any knee compartment.
5. Evidence of BMLs in index knee on magnetic resonance scanning (MRI)
6. Written informed consent

Previous participant inclusion criteria:
1. Age 50 years and over
2. Ambulatory (not wheel chair bound), and able and willing to comply with the intervention and follow up
3. Significant knee pain (have at least a score of 4 out of 10 on the primary symptom outcome of the trial, knee pain on a numerical rating scale (NRS Last week ≥4)
4. Evidence of significant OA on, x-ray – Kellgren Lawrence grade 2 or 3. Participants can have Kellgren and Lawrence grade 2 or 3 in any knee compartment.
5. Evidence of BMLs in index knee on magnetic resonance scanning (MRI)
6. Written informed consent

Participant type(s)
Patient

Age group
Adult

Sex
Both

Target number of participants
Planned Sample Size: 167; UK Sample Size: 167

Total final enrolment
58

Key exclusion criteria
Current participant exclusion criteria as of 02/10/2019:
1. History of septic arthritis affecting the index knee
2. History of inflammatory arthritis
3. Current treatment for gout and/or acute attack of gout within the previous 5 years
4. GFR < 35 ml/min
5. Vitamin D level of < 50 nmol/l
6. Abnormal liver function (ALT or AST > twice upper limit of normal) or elevated total bilirubin > 1.5 x ULN
7. Potential participants with a positive Hepatitis B surface antigen (HBsAg) or hepatitis C test result or a history of immune-deficiency diseases, including a positive HIV test result
8. History of malignancy in the past 5 years (other than basal cell carcinoma)
9. History of any solid organ or bone marrow transplant
10. History of alcohol abuse within previous 12 months
11. Known hypersensitivity to Latex
12. Hereditary problems of fructose intolerance
13. Non-healed dental / oral surgery
14. History of cellulitis of the lower limb within the last 5 years, osteonecrosis of the jaw, osteonecrosis of the external auditory meatus or atypical femoral fracture
15. Unhealed open soft tissue lesions in the mouth

16. History of invasive dental surgery in previous 6 months and/or invasive dental work planned in the next 6 months
17. Current anorexia nervosa, suspected bulimia (by history or physical examination) or obvious malnutrition
18. Active inflammatory bowel disease or current or recent malabsorption syndrome.
19. Hypo or hyperparathyroidism
20. Hypocalcemia (Calcium < LLN) / hypercalcemia (Ca > Upper Limit of Normal [ULN])
21. Osteoporosis on bone active therapy
22. Current or recent Osteomalacia (within the last 5 years) or other bone diseases which may affect bone metabolism (osteopetrosis / osteogenesis imperfecta)
23. Suspected knee fracture
24. Intra-articular therapy in the knee within the previous 3 months
25. Prior antiresorptive therapy with bisphosphonates in the last year (oral therapy) or 3 years (IV therapy)
26. Prior treatment in the last year with strontium ranelate / HRT / raloxifene / testosterone
27. Previous knee surgery (including cartilage surgery) or arthroscopy within 6 months on the affected knee
28. Planned knee or hip surgery in the next 6 months
29. Currently having physiotherapy for knee OA
30. Women of childbearing potential currently pregnant or planning pregnancy or breast feeding
31. Women of childbearing potential and refusal to use at least one highly effective form of contraception (methods that can achieve a failure rate of less than 1% per year when used consistently and correctly) and to continue until 5 months following intervention.
32. Concurrent life threatening illness or any other condition that in the opinion of the investigator would compromise participants safety or data integrity
33. Contraindication to MRI such as implants which prohibit safe use of MRI scan including cochlear implants / metal objects in the body including certain joint prosthesis, cardiac or neural pacemakers, hydrocephalus shunts, or certain types of intrauterine-device. Also trial knee circumference must not be >55cm or weight >125kg as these exceed the maximum MRI limits
34. Currently enrolled in or has not yet completed at least 1 month since ending other investigational device or drug trial(s), or potential participant is receiving other investigational agent(s)
35. Pain from sites outside the knee that are significantly more troublesome to the potential participant than knee pain and which significantly interferes with the ability of the potential participant to assess their knee pain
36. Unable to understand or retain the information provided regarding the trial procedures
37. Known hypersensitivity to denosumab or any ingredients of Prolia

Previous exclusion criteria as of 13/08/2018:
1. History of septic arthritis affecting the index knee
2. History of inflammatory arthritis
3. Current treatment for gout and/or acute attack of gout within the previous 5 years
4. GFR < 35 ml/min
5. Vitamin D level of < 50 nmol/l
6. Abnormal liver function (ALT or AST > twice upper limit of normal) or elevated total bilirubin > 1.5 x ULN
7. Potential participants with a positive Hepatitis B surface antigen (HBsAg) or hepatitis C test result or a history of immune-deficiency diseases, including a positive HIV test result
8. History of malignancy in the past 5 years (other than basal cell carcinoma)
9. History of any solid organ or bone marrow transplant
10. History of alcohol abuse within previous 12 months
11. Known hypersensitivity to Latex

12. Hereditary problems of fructose intolerance
13. Non-healed dental / oral surgery
14. History of cellulitis of the lower limb within the last 5 years, osteonecrosis of the jaw, osteonecrosis of the external auditory meatus or atypical femoral fracture
15. Unhealed open soft tissue lesions in the mouth
16. History of invasive dental surgery in previous 6 months
17. Invasive dental work planned in the next 6 months
18. Current anorexia nervosa, suspected bulimia (by history or physical examination) or obvious malnutrition
19. Active inflammatory bowel disease or current or recent malabsorption syndrome.
20. Hypo or hyperparathyroidism
21. Hypocalcemia (Calcium < LLN) / hypercalcemia (Ca > Upper Limit of Normal [ULN])
22. Osteoporosis on bone active therapy
23. Current or recent Osteomalacia (within the last 5 years)
24. Other bone diseases which may affect bone metabolism (osteopetrosis / osteogenesis imperfecta)
25. Intra-articular therapy in the knee within the previous 3 months
26. Prior antiresorptive therapy with bisphosphonates in the last year (oral therapy) or 3 years (IV therapy)
27. Prior treatment in the last year with strontium ranelate / HRT / raloxifene / testosterone
28. Previous knee surgery (including cartilage surgery) or arthroscopy within 6 months on the affected knee
29. Planned knee or hip surgery in the next 6 months
30. Currently having physiotherapy for knee OA
31. Women of childbearing potential currently pregnant or planning pregnancy or breastfeeding
32. Women of childbearing potential and refusal to use at least one highly effective form of contraception (methods that can achieve a failure rate of less than 1% per year when used consistently and correctly) and to continue until 5 months following intervention.
33. Concurrent life threatening illness or any other condition that in the opinion of the investigator would compromise participants safety or data integrity
34. Contraindication to MRI such as implants which prohibit safe use of MRI scan including cochlear implants / metal objects in the body including certain joint prosthesis, cardiac or neural pacemakers, hydrocephalus shunts, or certain types of intrauterine-device. Also trial knee circumference must not be >55cm or weight >125kg as these exceed the maximum MRI limits
35. Currently enrolled in or has not yet completed at least 1 month since ending other investigational device or drug trial(s), or potential participant is receiving other investigational agent(s)
36. Pain from sites outside the knee that are significantly more troublesome to the potential participant than knee pain and which significantly interferes with the ability of the potential participant to assess their knee pain.
37. Unable to take in, understand or retain the information provided regarding the trial procedures.
38. Known hypersensitivity to denosumab or any ingredients of Prolia

Previous exclusion criteria from 04/05/2018 to 13/08/2018:
1. History of septic arthritis, inflammatory arthritis or gout
2. Vitamin D level of <50 nmol/l
3. Abnormal liver function (ALT or AST >2x upper limit of normal) or elevated total bilirubin >1. 5x ULN
4. Potential participants with a positive Hepatitis B surface antigen (HBsAg) or hepatitis C test result or a history of immune-deficiency diseases, including a positive HIV test result
5. History of malignancy in the past 5 years (other than basal cell carcinoma)

6. History of any solid organ or bone marrow transplant
7. History of alcohol abuse within previous 12 months
8. Known hypersensitivity to Latex
9. Hereditary problems of fructose intolerance
10. Non-healed dental / oral surgery
11. History of cellulitis of the lower limb, osteonecrosis of the jaw or atypical femoral fractures
12. Unhealed open soft tissue lesions in the mouth
13. History of invasive dental surgery in previous 6 months
14. Invasive dental work planned in the next 6 months
15. Current anorexia nervosa, suspected bulimia (by history or physical examination) or obvious malnutrition
16. Current or recent (within 1 year of enrolment) inflammatory bowel disease or malabsorption syndrome.
17. Hypo or hyperparathyroidism
18. Hypocalcemia (Calcium < LLN) / hypercalcemia (Ca > Upper Limit of Normal [ULN])
19. Osteoporosis on bone active therapy
20. Osteomalacia
21. Other bone diseases which may affect bone metabolism (osteopetrosis / osteogenesis imperfecta)
22. Known intolerance to calcium supplements
23. Intra-articular therapy in the knee within the previous 3 months
24. Prior antiresorptive therapy with bisphosphonates in the last year (oral therapy) or 3 years (IV therapy)
25. Prior treatment in the last year with strontium ranelate / HRT / raloxifene / testosterone
26. Previous knee surgery (including cartilage surgery) or arthroscopy within 6 months on the affected knee
27. Planned knee or hip surgery in the next 6 months
28. Currently having physiotherapy for knee OA
29. Women of childbearing potential currently pregnant or planning pregnancy or breast feeding
30. Women of childbearing potential and refusal to use at least one highly effective form of contraception (methods that can achieve a failure rate of less than 1% per year when used consistently and correctly) and to continue until 5 months following intervention.
31. Concurrent life threatening illness or any other condition that in the opinion of the investigator would compromise participants safety or data integrity
32. Contraindication to MRI such as implants which prohibit safe use of MRI scan including cochlear implants / metal objects in the body including certain joint prosthesis, cardiac or neural pacemakers, hydrocephalus shunts, or certain types of intrauterine-device. Also trial knee circumference must not be >55cm or weight >125kg as these exceed the maximum MRI limits
33. Currently enrolled in or has not yet completed at least 1 month since ending other investigational device or drug trial(s), or potential participant is receiving other investigational agent(s)
34. Pain from sites outside the knee that are significantly more troublesome to the potential participant than knee pain and which significantly interferes with the ability of the potential participant to assess their knee pain.
35. Unable to take in, understand or retain the information provided regarding the trial procedures.
36. Known hypersensitivity to denosumab or any ingredients of Prolia

Original exclusion criteria:
1. History of septic arthritis, inflammatory arthritis or gout
2. Vitamin D level of < 50 nmol/l
3. Abnormal liver function (ALT or AST > twice upper limit of normal) or elevated total bilirubin >

1.5 x ULN
4. Potential participants with a positive Hepatitis B surface antigen (HBsAg) or hepatitis C test result or a history of immune-deficiency diseases, including a positive HIV test result
5. History of malignancy in the past 5 years (other than basal cell carcinoma)
6. History of any solid organ or bone marrow transplant
7. History of alcohol abuse within previous 12 months
8. Known hypersensitivity to Latex
9. Hereditary problems of fructose intolerance
10. Non-healed dental / oral surgery
11. History of cellulitis of the lower limb, osteonecrosis of the jaw or atypical femoral fractures
12. History of invasive dental surgery in previous 6 months
13. Invasive dental work planned in the 6 months
14. Current anorexia nervosa, suspected bulimia (by history or physical examination) or obvious malnutrition
15. Current or recent (within 1 year of enrolment) inflammatory bowel disease or malabsorption syndrome.
16. Hypo or hyperparathyroidism
17. Hypocalcemia (Calcium < LLN) / hypercalcemia (Ca > Upper Limit of Normal [ULN])
18. Osteoporosis on bone active therapy
19. Osteomalacia
20. Other bone diseases which may affect bone metabolism (osteopetrosis / osteogenesis imperfecta)
21. Known intolerance to calcium supplements
22. Intra-articular therapy in the knee within the previous 3 months
23. Prior antiresorptive therapy with bisphosphonates in the last year (oral therapy) or 3 years (IV therapy)
24. Prior treatment in the last year with strontium ranelate / HRT / raloxifene / testosterone
25. Previous knee surgery (including cartilage surgery) or arthroscopy within 6 months on the affected knee
26. Planned knee or hip surgery in the next 6 months
27. Currently having physiotherapy for knee OA
28. Women of childbearing potential currently pregnant or planning pregnancy or breast feeding
29. Women of childbearing potential and refusal to use 2 highly effective forms of contraception and to continue until 5 months following intervention
30. Concurrent life threatening illness or any other condition that in the opinion of the investigator would compromise participants safety or data integrity
31. Contraindication to MRI such as implants which prohibit safe use of MRI scan including cochlear implants / metal objects in the body including certain joint prosthesis, cardiac or neural pacemakers, hydrocephalus shunts, or certain types of intrauterine-device. Also trial knee circumference must not be > 55cm or weight > 125kg as these exceed the maximum MRI limits.
32. Currently enrolled in or has not yet completed at least 1 month since ending other investigational device or drug trial(s), or potential participant is receiving other investigational agent(s)
33. Pain from sites outside the knee that are significantly more troublesome to the potential participant than knee pain and which significantly interferes with the ability of the potential participant to assess their knee pain
34. Unable to take in, understand or retain the information provided regarding the trial procedures

Date of first enrolment
01/07/2017

Date of final enrolment
26/02/2020

Locations

Countries of recruitment
England

United Kingdom

Study participating centre
Salford Royal Hospital
Salford Royal NHS Foundation Trust
Stott Lane
Salford
United Kingdom
M6 8HD

Sponsor information

Organisation
The University of Manchester

Sponsor details
Oxford Road
Manchester
England
United Kingdom
M13 9PL
+44 (0)161 275 2725
Clinicaltrials@manchester.ac.uk

Sponsor type
University/education

ROR
https://ror.org/027m9bs27

Funder(s)

Funder type
Charity

Funder Name
Arthritis Research UK

Alternative Name(s)

Funding Body Type
Private sector organisation

Funding Body Subtype
Other non-profit organizations

Location
United Kingdom

Results and Publications

Publication and dissemination plan
Planned publication in a high-impact peer reviewed journal.

Intention to publish date
31/12/2022

Individual participant data (IPD) sharing plan
Anonymised patient-level data may be shared by application to the Principal Investigator. This would be subject to the proposed research being in accordance with arrangements for data sharing in the Participant Information Sheet and Consent Form; and any necessary data sharing contracts and ethical approvals for the research being in place.

IPD sharing plan summary
Available on request

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Basic results	version 1.0	16/12/2021	21/12/2021	No	No
Protocol file	version 2.7	16/05/2019	22/08/2022	No	No
HRA research summary			28/06/2023	No	No