The effect of denosumab on muscle and strength and insulin sensitivity

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List of abbreviations

AE = adverse events

AGEs = advanced glycation end products

BAP = Bone alkaline phosphatase

BMD = Bone mineral density

CTIS = The Clinical Trials Information System

CTX = Carboxy-terminal collagen crosslinks

DXA = Dual-energy x-ray absorptiometry

eCRF = Electronic case report form

GP = general practitioner

Hb1Ac = Hemoglobin A1c

HOMA-IR = Homeostatic Model Assessment for Insulin Resistance

OGTT = Glucose tolerance test

OPG = Osteoprotegerin

PINP = Procollagen type I N-terminal propeptide

PTH = Parathyroid hormone

RANKL = receptor-activator of nuclear factor kappa-B ligand

REDCap = Research Electronic Data Capture

TRAcP-5b = tartrate-resistant acid phosphatase type 5b

SAE = serious adverse events

SAR = serious adverse reactions

SUSAR = suspected unexpected serious adverse reactions (SUSAR)

TSH = Thyroid stimulating hormone

VFA = Vertebral fracture assessment

25-OH-vitamin D = 25-hydroxy-vitamin D

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Monitoring

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_____
Sponsor

_____

Investigator

Background

Denosumab is an antibody against receptor-activator of nuclear factor kappa-B ligand (RANKL) that prevents recruitment and differentiation of mature osteoclasts [1]. Treatment with denosumab markedly decreases bone resorption, increases bone mineral density (BMD), and reduces the risk of vertebral as well as non-vertebral and hip fractures [2], [3]. Osteoclasts produce dipeptidyl peptidase-4 (DPP-4) that degrades glucagon-like peptide-1 (GLP-1) and GLP-1 stimulates insulin production [4]. In accordance with this, animal models have shown a beneficial effect of denosumab on glucose metabolism [5]. However, data from clinical studies in patients with osteoporosis are limited and the results inconsistent. In a small, randomised trial with 52 healthy postmenopausal women, treatment with denosumab for 12 months reduced DPP-4 and increased GLP-1 compared to placebo but no effect was seen on insulin or fasting glucose levels [4]. In the same publication, the authors conducted a non-randomized, observational study in osteoporotic patients with diabetes mellitus or prediabetes that were treated with either denosumab, bisphosphonates, or calcium + vitamin D at the discretion of their physician. Here, treatment with denosumab significantly reduced fasting glucose after 6 months and HbA1c after 12 months compared to bisphosphonates or calcium + vitamin D [4]. Similar findings were seen in another observational study with 20 patients with diabetes [6]. On the other hand, a post hoc analysis of the FREEDOM trial did not find a general effect of denosumab on fasting glucose in postmenopausal women with self-reported diabetes or prediabetes, but only reported a small decrease in fasting glucose in denosumab treated women with diabetes not treated with antidiabetics [7]. This is in line with three small observational studies, in which no clinically relevant effect of denosumab on fasting glucose, insulin level or homeostatic model assessment for insulin resistance (HOMA-IR) was identified [8]–[10].

Overall, the heterogeneity across the studies is large, most of the trials are observational studies and the results are inconsistent. Therefore, randomized, controlled trials are warranted to further elucidate this.

Denosumab has also been shown to improve muscle strength compared to placebo in animal models [5], however, data from human studies is limited. In an observational study, denosumab decreased the risk of falls and improved sarcopenia measures in 135 patients with osteoporosis compared to 272 patients treated with alendronate or zoledronate assessed at treatment initiation and after 5 years for denosumab and alendronate and 3 years for zoledronate [11]. All outcome measures worsened one years after denosumab discontinuation. In another prospective observational study with 18 postmenopausal women, denosumab treatment for an average of three years improved appendicular lean mass and handgrip strength compared to treatment with bisphosphates or placebo [5]. This is in line with two additional observational studies, in which denosumab improved muscle strength after 6 - 17 months compared to bisphosphonates or vitamin D [12], [13].

None of the studies evaluating the effect of denosumab on muscle strength are randomised controlled trials, the outcome measures are different and the follow up visits few. Also, none of the studies controlled for exercise.

We therefore want to conduct a randomized, placebo controlled prospective trial evaluating the effect of denosumab on insulin sensitivity and muscle strength.

Aims

We want to investigate the effect of denosumab on muscle mass, muscle strength and insulin sensitivity.

Study design, population and methods

Design

The study is a randomized double-blind, interventional study in 40 postmenopausal with diabetes mellitus type 2. The patients will be randomized at baseline to denosumab 60 mg (n=20) or placebo (n=20), which will administrated at baseline and month 6.

The study site is Department of Endocrinology and Internal Medicine, Aarhus University Hospital.

Co-primary endpoints

- Changes in muscle mass and muscle strength from baseline to month 12.
- Changes in insulin sensitivity (Hb1Ac, HOMA-IR, fasting glucose, oral glucose tolerance test (OGTT)) from baseline to month 12.

Secondary endpoints

- Changes in DPP-4 and GLP-1 from baseline to month 12.
- Changes in carboxy-terminal collagen crosslinks (CTX) and procollagen type I N-terminal propeptide (PINP) from baseline to month 12.
- Change in lumbar spine BMD from baseline to month 12.
- Change in advanced glycation end products (AGEs) from baseline to month 12.
- Changes in muscle strength from baseline to month 1 and 3.
- Changes in insulin sensitivity (Hb1Ac, HOMA-IR, and fasting glucose) from baseline to month 1 and 3

Study population

Inclusion criteria

- Postmenopausal women (postmenopausal for at least two years)
- Age ≥ 40 years
- BMD T-score ≥ -2.0 (lumbar spine, total hip or femoral neck)
- At least 2 lumbar vertebrae that can be evaluated by dual-energy x-ray absorptiometry (DXA)
- Diabetes Mellitus type 2
- Treatment with metformin as monotherapy

Exclusion criteria

- Treatment for osteoporosis at any time
- Other antidiabetic medication than metformin
- Low-energy vertebral fractures at any time

- Low-energy hip fracture at any time
- Ongoing treatment with systemic glucocorticoids
- Metabolic bone disease (for example osteogenesis imperfecta, Paget's disease of bone, hyperparathyroidism)
- Treatment affecting bone, calcium metabolism or muscle
- Active cancer within the last 5 years with the exception of basal cell skin cancer
- Estimated glomerular filtration rate (eGFR) ≤ 35 mL/min
- Unable to read and understand Danish
- Immobility

Study plan

Groups 1 + 2	**Screening**	**Baseline**	**M1 ± 7 days**	**M3 ± 7 days**	**M6 ± 7 days**	**M12 ± 14 days**
Informed consent	X					
Medical history	X					
Questionnaires		X	X	X	X	X
Fracture history	X				X	X
Physical examination	X					
Biochemical markers of bone turnover		X	X	X	X	X
Biochemical markers of diseases affecting bone metabolism	X				X	X
Hb1Ac, fasting glucose, HOMA-IR	X		X	X	X	X
OGTT		X			X	X
AGEs (skin autofluorescence)		X	X	X	X	X
Muscle strength		X	X	X	X	X
Whole-body DXA	X				X	X
DXA	X				X	X
Vertebral fracture assessment (VFA)	X					X
Placebo / denosumab		X			X	

Investigations

Questionnaires: to assess exercise and calorie intake. The participants will be asked not to change their diet or exercise habits during the study period.

Biochemical markers of bone turnover and metabolism: bone alkaline phosphatase, osteocalcin, PINP, CTX, sclerostin, tartrate-resistant acid phosphatase-5b (TRAPc-5b), GLP-1 and DPP-4. Markers will be analysed in batch at the end of the study. The samples will be collected in the morning after a minimum of eight hours of fasting.

Markers of diseases affecting bone metabolism: calcium, phosphate, magnesium, 25-OH-vitamin D, parathyroid hormone (PTH), creatinine, alkaline phosphatase and thyroid stimulating hormone (TSH).

Bone mass: BMD will be measured by a DXA scan of the lumbar spine (L1-L4) and left hip, using a Hologic Discovery scanner. Right hip will be scanned in case of a prosthetic left hip.

Incident vertebral fractures: will be investigated using the VFA tool on the Hologic Discovery scanner or spinal x-ray at the investigator's discretion.

Fracture history: Participants will be questioned about fracture history. Information will be confirmed using discharge notes from hospitals.

Muscle mass: Lean body mass will be measured by whole-body DXA.

Muscle strength: will be measured as handgrip strength, muscle strength over the knee and elbow joints, chair rising test, test of balance and timed-up-and-go.

Insulin sensitivity: will be assessed by Hb1Ac, HOMA-IR, fasting glucose and OGTT.

AGEs: skin autofluorescence is a non-invasive measure reflecting the accumulation of AGEs in the skin. Skin autofluorescence will be measured using the AGE reader. Two subsequent measurements will be conducted on the volar side of the lower dominant arm.

Treatment: A subcutaneous injection of 60 mg denosumab (Xgeva, 0.9 ml) or placebo (saline 0.9 ml) will be administered at baseline and month 6. Before denosumab can be administrated calcium, creatinine and eGFR must be available and eGFR > 35 ml/min.

Duration of study

Included patients will be part of the study for to 12 months (month 12 = last visit). The primary endpoints will be investigated 12 months after baseline. The participants will receive a letter from the investigator after the termination of the study with information about the study results.

Fertility and pregnancy

Pregnancy testing and precautions concerning female fertility will not be relevant since the women participating in the study are postmenopausal.

Randomization and blinding

The patients will be randomized to denosumab or placebo at baseline. Treatment will be double-blinded. The investigational drug is denosumab. Xgeva will be used (appendix 1). Each vial of Xgeva contains 120 mg of denosumab in 1.7 mL of solution (70 mg/mL). Participants will be given a dose of denosumab 60 mg (Xgeva, 0.9 ml, subcutaneous injection), which is the standard dose for treatment of osteoporosis. The placebo is saline 0.9 ml.

Trained medical staff, not otherwise involved in the trial will prepare an identical syringe with either 0.9 ml of denosumab or saline, which will be labelled according to GMP and GCP standards. The drug label will display name of sponsor, study and investigator, participant ID, pharmaceutical form (solution for injection), route of administration (subcutaneous), quantity of dosage units (0.9 ml) and investigational drug (denosumab or placebo). Denosumab/placebo will be administrated by the sponsor or investigator as a single subcutaneous injection in the abdomen. The sponsor is responsible for the treatment.

DXA results at month 6 results will be unknown to the investigators and patients during the study. In case of a significant decrease (>5%) in BMD at any site, the investigator will be informed.

The participants will be randomized in blocks of 6. In case of dropouts the randomization codes will be reused for new participants. The randomization code will be generated in REDCap. The randomization code will be unknown to investigators, all investigational staff and patients. The sponsor will have access to the code in REDCap. The code can be revealed if the sponsor and investigator believe that it will affect the outcome of a seriously ill patient participating in the study. It will be possible to reveal the code for individual participants. Unblinding will be done after the last patient has been to the last visit and statistical analysis of the study results have been finalised.

Investigational drug, drug ordering and accountability, storage conditions, and technical problems

The investigational drug is denosumab. Xgeva will be used (appendix 1). Participants will be given a dose of denosumab 60 mg, which is the standard dose for treatment of osteoporosis. Known side effects to denosumab includes injection site reaction, musculoskeletal pain, obstipation, abdominal pain, hypocalcaemia, atypical femur fracture, and osteonecrosis of the jaw (appendix 1, section 4.8).

The placebo is saline 0.9 ml. The patients treated with placebo will not be subject to additional risks of serious or irreversible harm as a result of not receiving the active drug.

The active drug and placebo will be supplied by the hospital pharmacy and delivered directly to the investigational site, where standardized quality control will be performed. Drug accountability will be done using lists in accordance with GCP. The active drug and placebo will be stored according to its labelled storage conditions. The drug will be stored in a locked refrigerator at 2-8 degrees. In case of technical problems with the drug it will be replaced, and the drug will be returned to the pharmacy. Technical problems include discoloration, particles or contamination, leakage, or cracks. The investigator is accountable for the drug. Date and time of start and finish of the administration of the investigational drug/placebo will be noted. Used drug/placebo containers will be disposed of locally. Drug/placebo will be administered according to the randomization.

As part of the standard treatment of osteopenia a daily intake of 1000 mg calcium and 38 ug vitamin D will be secured by supplementation.

Data management

Source data identification and verification

Source data will be entered into the eCRF in REDCap. The investigator and the monitor from the GCP-unit at Aarhus University Hospital will perform data verification.

During the study, information on DXA and biochemistry will be found in the patient's electronic medical records and treatment with denosumab/placebo will be listed in the records.

eCRF in REDCap

The purpose of eCRF is to report all the information required by the protocol to the individual trial participants. Completion of eCRF will begin with the recruitment of the participants and filled in continuously throughout the trial by the investigators (or persons appointed by the investigators who are either experienced in clinical trials or who will receive training prior to the assignment). eCRF is the source document for trial data that is written directly into the eCRF. Source

data, which is recorded directly in the eCRFs, includes protocol-specific measurements that are not relevant in the patient's record. eCRF is managed by REDCap.

Subject data protection

Access to the eCRFs will be limited to the investigators and other healthcare professionals involved in this study. Data from the eCRFs can be passed on to healthcare professionals at the hospital who are in charge of the treatment of the participants. Data may also be passed on to the monitor from the GCP-unit and inspectors from the Danish Health authorities. Any printouts of the eCRFs will be kept behind locked doors after working hours.

Data handling

When data analyses are finalized, the data will be converted to a pseudonymized form using participation numbers only, and names and social security numbers will be removed.

Statistical analysis and power calculation

Baseline characteristics of the treatment groups will be presented using descriptive analysis and compared using unpaired t-tests. Changes in muscle mass, muscle strength, AGEs, insulin sensitivity, BMD, bone markers will be compared within and between groups using mixed model analysis.

In a small study, treatment with denosumab improved muscle function up to 14% after 6 months [12], however, power calculations cannot be conducted based on the data available. Weivoda et al. found a reduction in HOMA-IR of 5.9% (SD 8,1) in patients with osteoporosis and diabetes mellitus type 2 or prediabetes who were treated with denosumab after 6 months [4]. Our hypothesis is that treatment with denosumab can improve muscle strength and insulin sensitivity. Seventeen patients will be needed to demonstrate a reduction in HOMA-IR ≥ 6 % using a paired-sample t-test with a power of 80% and level of significance of 5%. To account for dropouts n is increased to 20 in each group.

The statistical analyses will be performed by researchers blinded to treatment allocation.

Recruitment of participants

The patients will be recruited from the outpatient clinic and the DXA unit at the Department of Endocrinology and Internal Medicine, Aarhus University Hospital. The staff will be informed about the study including inclusion and exclusion criteria. Potential participants will be approached during visits or by letter (appendix 2). If a patient is interested in receiving further information, she will receive written information about the project (appendix 3).

In addition, women living in Denmark, who have redeemed at least two prescriptions for metformin within the last six months and no prescription for other antidiabetic medication or anti-osteoporotic medication will be identified by The Danish Health Data Authority (Sundhedsdatastyrelsen), through The Medicine Statistics Register (Lægemiddelstatistikregisteret) and will be approached by letter (appendix 2).

We will advertise on the webpage www.forsøgsperson.dk (appendix 4). Potential participants who respond to letters or advertisements will be pre-screened in their electronic medical records to evaluate health information, medication, and biochemistry relevant to in- or exclusion criteria and will be sent written information about the trial (appendix 3).

Subsequently, all potential participants will be invited to a meeting with one of the investigators. A family member or a friend are welcome to participate in the meeting as well. The person conveying information and collecting consent will be 1) a qualified medical doctor, or 2) if it is not the investigator him/herself, there will be a written agreement between the investigator and the medical doctor taking on this task. At this meeting that will take place in an office in the hospital the patient will be informed orally about the study aims and design, the study procedures and the potential risks. The patient will be encouraged to ask questions. The patient will be informed about the right to withdraw the consent at any time without providing any reason. In case of incidental health findings during screening or during the study, the patient will be informed, encouraged to contact their general practitioner or referred to a specialist.
Afterwards the potential participant will be given up to 14 days to consider whether they wish to participate in the study, before they sign the consent form. The participants will not take part in the study before the consent form has been signed. Inclusion in the study will be noted in the electronic medical records.

Biobanks

A research biobank will be made during the study. A total of 200 ml blood (40 ml at each visit) from all participants will be sampled. The blood samples will be analysed in batches. Access to the research biobank is controlled by the principal investigator. After the trial has ended and the main publications have been accepted for publication, the remaining blood samples will be transferred to biobanks for future research at Aarhus University Hospital in pseudonymized form (ID-number only) and stored for a maximum of twenty years before destruction. Participants will be informed about the biobanks for future research and that blood samples can be destroyed at all times on request of the participant. A refusal of consent, or a withdrawal of consent at a later time, will be documented in the eCRF and the blood samples will be destroyed. The material stored in the biobanks will only be used for future research after approval from the The Ethics Committee System.

Assessment of safety

Definition of adverse events (AE)

Any untoward medical occurrence in a patient or clinical investigation subject administered/using a product and which does not necessarily have to have a causal relationship with this treatment. An adverse event can therefore be any unfavourable and unintended sign (including a clinically relevant abnormal laboratory finding), symptom, or disease temporally associated with the use of a product, whether or not considered related to the product.
The severity is assessed as follows:

- Mild: Awareness of sign or symptom, but easily tolerated.
- Moderate: Discomfort enough to cause interference with usual activity.
- Severe: Incapacitating with inability to work or do usual activity.

Relationship to study drug is defined as follows:

- Unrelated: The adverse event is clearly not related to the study drug and is clearly related to an underlying disease, environmental or toxic factors, or other drug or therapy or the adverse event does not follow a reasonable temporal sequence after study drug.
- Possible: The adverse event occurred in a reasonable time after study drug administration but could be related to an underlying disease, environmental or toxic factors, or other drug or therapy.
- Probable: The adverse event occurred in a reasonable time after study drug administration and is unlikely to be related to an underlying disease, environmental or toxic factors, or other drug or therapy. The event may respond to stopping the study drug.

Outcomes are defined as “recovered”, “recovering”, “recovered with sequelae”, “not recovered”, “fatal”, or “unknown”.

Assessment of AEs

At baseline a thoroughly physical examination of the participants and questioning concerning any conditions or diseases will take place. This way the investigators will be able to evaluate possible changes throughout the study. Patients will be interviewed about the occurrence of AEs at each visit from the first trial related activity after the subject has signed the informed consent. Subjects that experience adverse events or develop a disease during the trial period will be managed until the condition is cured or stationary. If this is not the case at the end of the study, subjects will be referred to a relevant physician, e.g. the general practitioner or a specialist, for follow-up. All queries related to these AEs will be resolved. Cases of chronic conditions, cancer or AEs ongoing at time of death (where death is due to another AE) will be closed with the outcome “recovering/resolving” or “not recovered/not resolved”. Cases can be closed with the outcome of “recovering/resolving” when the subject has completed the follow up period and is expected by the investigator to recover.

The decision to unblind participants during emergency situations is the sole responsibility of the investigator. Thus, the investigator will have access to the randomization codes at all times.

Annual safety report will be submitted through the CTIS-system, with a report on the safety of each investigational medicinal product used in the study.

Definition of serious adverse events (SAE)

Any untoward medical occurrence that:

- Results in death
- Is life-threatening ("life threatening" in the definition of SAE refers to an event in which the subject was at risk of death at the time of the event. It does not refer to an event which hypothetically might have caused death if it was more severe)
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect

- Is an important medical event that may not result in death, be life-threatening, or require hospitalization but may be considered a serious adverse event when, based upon appropriate medical judgment, it may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

Definition of serious adverse reactions (SAR)

A SAR is an adverse event, which fulfil both the criteria for a SAE and the criteria for an adverse reaction. An adverse reaction is a response to a medicinal product which is noxious and unintended, and for which the causal relationship between the product and the adverse event is suspected (judged possible or probable by the sponsor or the investigator). A serious adverse event will be evaluated according to the public assessment reports of denosumab by the European Medicines Agency and Danish National Board of Health (appendix 1).

Definition of suspected unexpected serious adverse reactions (SUSAR)

A SAR, where the nature, severity or outcome of which is not consistent with the reference safety information.

Reporting of SAEs, SARs, and SUSARs

SAEs and SARs will be reported to the sponsor by automated emails generated by REDCap. The information about SAEs and SARs should be entered into REDCap no later than 24 hours after the investigator has become aware of them. SUSARs that have been deadly or life threatening will be reported via EudraVigilance, no later than seven days after sponsor is notified. No later than eight days after this notification the Danish Medicines Agency will be notified about follow-up procedures and information. Other SUSARs will be reported after no more than 15 days. In addition, a yearly report on SAEs and SARs will be sent to the Danish Medicines Agency and the Medical Research Ethics Committee (MREC).

All SAEs will be managed until the outcome of the event is “recovered”, “recovered with sequelae” or “fatal” and until all queries have been resolved. The follow up information on SAEs will only include new (corrections or new or additional) information and will be reported within 24 hours of obtaining knowledge of the information. This will also be the case with previously non-serious AEs, which subsequently become SAEs.

Safety reporting requirements

When reporting events, the following parameters will be recorded:

- Study name
- Event start/stop date
- Severity
- Seriousness
- Patient identification (e.g. subject number, initials, sex, age)
- Event (preferably a diagnosis)

- Drug
- Reporter identification (e.g. name, or initials)
- Causality
- Outcome

All AEs will be registered in REDCap. When a SAE/SAR is registered in REDCap an email will be send to the sponsor.

Insurance

Patients are covered by a publicly funded compensation scheme and participants are covered by the blue European Health Insurance Card when travelling in Europe.

Termination of the study

The study will be stopped if new information about serious or life-threatening side effects occurring at a frequency that may cause general concern about the safety of denosumab comes to the investigator's knowledge. The study will be terminated for single participants in the case of patient decision or if the investigator finds it in the best interest of the participant from a medical and safety perspective. If a patient must be terminated early from the study or decides to withdraw the consent to participate, the patient will be asked permission to seek information about future fractures occurring before the end of the trial.

The patient files will be kept at site for up to 15 years after completion of the study. Only the principal investigator and co-investigators will have access to the files.

Perspectives

Of the antiresorptive treatments approved, denosumab provides the best BMD improvement on treatment and a strong protection against fractures. Small studies have indicated that denosumab may have beneficial effects on muscle strength and insulin sensitivity. Muscle mass and strength as well as diabetes are important risk factors for both falls and fractures and therefore of great importance for patients with osteoporosis. The study will provide information about additional potential benefits of denosumab and help qualify the choice of treatment in the individual patients.

Improvement of the understanding of the use of denosumab in clinical practice will be important for optimizing the use of denosumab in the long-term management of osteoporosis.

Safety and ethical considerations

Puncture of veins for blood sampling can result in a bruise and very rarely in infection. The DXA examinations result in radiation doses of maximum 30 µSv. This increases the risk of cancer by 0.00015% and the lifetime risk of cancer increases from 25% to 25.00015%. Known side effects to denosumab includes injection site reaction, musculoskeletal pain, obstipation, abdominal pain, hypocalcaemia, atypical femur fracture, and osteonecrosis of the jaw. For a more detailed list of the known side effect see section 4,8 in the public assessment report of denosumab by the Danish National Board of Health (appendix 1).

Denosumab is cleared from the circulation within six months and does not adhere to bone meaning that after discontinuation the suppression of bone resorption ceases [14]. In patients discontinuing long-term denosumab, bone turnover does not merely return to pre-treatment level but increases above what has been termed "rebound activation of bone turnover", which have been associated with bone loss and increased fracture risk [14], [15]. This is not the case for patients discontinuing short term denosumab. Clinical trials and observational studies have shown that treatment for one year with alendronate or one infusion of zoledronate may prevent the rebound phenomenon in patients who have been treated for a few years with denosumab [16], [17]. The patients in the current study will only receive two injections of denosumab, and we will evaluate bone turnover by CTX and DXA at month 12. In case of increased bone turnover, we will offer the patient subsequent antiresorptive treatment with follow up in our outpatient clinic or at the patient's GP.
We believe that the risks associated with participating in this study are limited and we believe the potential gains from this study outweigh the risks.

Economy

The study is initiated by the investigators. The Danish Osteoporosis Foundation has granted financial support (77.144 dkr) and The Diabetes and Endocrine Academy, which is funded by the Novo Nordisk Foundation, (240.000 dkr, grant number NNF22SA0079901). Participants will have expenses for transport reimbursed but will not otherwise be paid to participate.

Publications

The results of the study will be published in an international scientific journal. All results including inconclusive, positive, and negative results will be accessible to the public after the study has ended. As soon as possible and no later than one year after the trial has ended, the trial results will be submitted to the CTIS-portal.
After completion of the study, the participants will receive written information about the results. The participants can seek further information about the project by contacting the investigator.

Monitoring

The study is conducted according to the final version of the protocol and according to the Helsinki declaration, GCP guidelines, the Regulation, and the Danish Health Law. Treatment with placebo will be administered according to the Helsinki declaration article 33. The processing of data is carried out in accordance with the GDPR and the Danish Data Protection Act. The study will not be initiated until approval has been given from the Medical Research Ethics Committees (MREC), and the Danish Medicines Agency. The study will be monitored by the local GCP unit at Aarhus University Hospitals (Aarhus University, Palle Juul-Jensens Boulevard 99, 8200 Aarhus N, Denmark). The study will be conducted in compliance with GCP procedures for quality control and quality assurance.

Research plan and facilities

March 2024 – August 2024: Recruitment of participants

March 2024 – September 2025: Clinical trial on-going and collection of data

November 2025 – January 2026: Analysis and publication

We have all the facilities for the clinical study at the department of Endocrinology and Internal Medicine at Aarhus University Hospital. We have experienced research nurses and laboratory technicians, and we have access to analyses of biochemical markers at the Departments of Clinical Biochemistry, Aarhus University Hospital.

Appendices

Appendix 1: SPC for Xgeva

Appendix 2: Letter to potential participants

Appendix 3: Patient information

Appendix 4: Advertisement

References

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