Treatment with zoledronate subsequent to denosumab in osteoporosis: a randomized trial

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Monitoring

The study is monitored by the local GCP unit at Aalborg and Aarhus University Hospital, Aarhus University, Olof Palmes Allé 15, 8200 Aarhus N, Denmark.

Background

Osteoporosis is most commonly treated with anti-resorptive therapy. The two most widely used anti-resorptive agents are bisphosphonates (either alendronate or zoledronic acid) and denosumab. Bisphosphonates adhere to the bone and when taken up by the osteoclasts, bisphosphonates interfere with their cytoskeleton and the osteoclasts become unable to resorb bone and may undergo apoptosis [1]. Denosumab is an antibody against receptor-activator of nuclear factor kappa-B ligand (RANKL) that prevents recruitment and differentiation of mature osteoclasts [2]. Both agents markedly decrease bone resorption and fracture risk [3-5] First line treatment is alendronate that by far is the cheapest. In Denmark denosumab can only be reimbursed if the patient cannot take alendronate due to side effects, treatment failure or contra indications why denosumab is second line therapy. Zoledronic acid is administered intravenously and therefore in clinical practice almost exclusively administered in hospitals, which limits its use.

It has become evident that long-term anti-resorptive therapy (bisphosphonates and denosumab) may lead to serious side effects such as atypical femoral fractures [6] or osteonecrosis of the jaw [7]. This has obviated the need for an evidence-based assessment of the balance between long-term benefits and risks. The adhesion of bisphosphonates to bone is very strong meaning that the biological half-life is years and that the effect on bone remains long after administration [8]. In accordance with this the alendronate extension study showed that despite stopping treatment after five years the anti-fracture efficacy regarding non-vertebral and radiological vertebral fractures persists for an additional five years in patients with BMD T-score > -2.5 at the femoral neck, no fractures during treatment, and no previous vertebral fracture [9-10]. Zoledronic acid adheres even stronger to bone than alendronate and is administered intravenously once yearly. Zoledronic acid treatment can be discontinued after three years based on the same criteria as alendronate [11].

Compared to bisphosphonates the pharmacokinetics of denosumab is completely different. Denosumab is cleared within six months and does not adhere to bone meaning that after discontinuation of denosumab bone resorption increases again. In addition, the bone mass gained during two years of therapy is completely lost within one year after discontinuation [12], and recent evidence even suggests that discontinuation of long-term therapy may lead to hypercalcemia [13] and multiple vertebral fractures [14-17] due to increased bone-turnover. At present denosumab treatment is considered to be life-long.

Aims

To investigate if infusion of zoledronic acid can prevent increases in bone turnover and bone loss in patients previously treated with denosumab and if there is difference between infusing zoledronic acid at six or nine months after the last injection of denosumab or when bone turnover is increased. The reason for investigating different time points for the infusion of zoledronic acid is that if bone remodelling is strongly suppressed by the previous denosumab treatment, bisphosphonate may not adhere well enough to the bone surface to inhibit resorption once the effect of denosumab wears off. It has been demonstrated that some patients still have completely suppressed markers of bone turnover six months after the last injection but also that most patients have regained some resorptive activity three months later [12].

Study population and methods

Design

A randomized open label, interventional study in 60 patients investigating if treatment with zoledronic acid prevents bone loss after denosumab treatment when administrated six (6-month group, n=20) or nine months (n=20, 9-month

group) after last injection of denosumab or when bone turnover is increased (n=20, observation group). Forty patients will be allocated to the two intervention groups and 20 patients will be followed without treatment for up to 12 months after the last denosumab treatment. The patients in the observation group and the nine months group will be monitored monthly and if p-carboxy-terminal collagen crosslinks[1] (p-CTX) increases above 1.26ug/l (50% above the normal range[2] for postmenopausal women and elderly men) infusion of zoledronic acid will be administered. Furthermore, a DXA scan (lumbar spine and hip sites) will be performed after three months in the observation group. If BMD has decreased more than 5% at the lumbar spine or total hip, infusion of zoledronic acid will be administered. Finally, if a patient in the 9 months group or the in the observation group suffers an osteoporotic clinical vertebral or hip fracture, infusion of zoledronic acid will be administered.

The patients will be given a single infusion of zoledronic acid as the increase in bone turnover seen after stopping denosumab seems most prominent in the first year [12]. The patients will be monitored with DXA 6, 12 and 24 months after the infusion of zoledronic acid. Zoledronic acid will be re-administered if BMD has decreased more than 5% at the lumbar spine, total hip or femoral neck.

If p-CTX increases above 1.26 ug/l during the 2nd year a second infusion of zoledronic acid will be administered.

Co-primary endpoint

- Change in lumbar spine BMD from baseline to 6 months after the zoledronic acid infusion.
- The proportion of patients who fails to maintain BMD (total hip, femoral neck and spine). Failure is defined as ≥ 3 % BMD loss at the lumbar spine or ≥ 5 % BMD loss at the femoral neck or total hip.

Secondary endpoints

- Changes in total hip, femoral neck and lumbar spine BMD from baseline to one year after the zoledronic acid infusion.
- Changes in total hip, femoral neck and lumbar spine BMD from baseline to two years after the zoledronic acid infusion.
- Changes in trabecular bone volume fraction (bone volume/tissue volume, BV/TV) and cortical porosity measured by high-resolution peripheral quantitative computed tomography (HR-pQCT) scan at the radius and tibia from baseline to one year after the zoledronic acid infusion.
- Changes in p-CTX and p-procollagen type I N-terminal propeptide[3] (p-PINP) from baseline to six months after the zoledronic acid infusion.
- Changes in p-CTX and p-PINP from baseline to 12 months after the zoledronic acid infusion.
- Morphometric vertebral fractures assessed by vertebral fracture assessment (VFA) one and two years after the zoledronic acid infusion.

[1] Electrochemiluminescence immunoassay (ECLIA) will be used.

[2] Reference range: Women 30-50 years: 0,04 - 0,59 µg/l. Women > 50 years: 0.03-0.83 µg/l. Men 30-50 years: 0,09 - 0,63 µg/l. Men 50-70 years: 0.04-0.84 µg/l. Men > 70 years: 0,08 – 1,05 µg/l.

[3] ECLIA will be used.

Study population

Inclusion criteria

- Postmenopausal women (postmenopausal for at least two years)
- Men above 50 years
- Treatment for at least two years with denosumab
- Last denosumab injection less than five months ago

Exclusion criteria

- Low-energy vertebral fracture at any time
- Low-energy hip fracture within the last 12 months
- BMD T-score < -2,5 (lumbar spine, total hip or femoral neck)
- Alendronate treatment for more than three years prior to denosumab treatment
- Ongoing treatment with glucocorticoids
- Metabolic bone disease
- Hormone replacement therapy
- Cancer
- Estimated glomerular filtration rate (eGFR) < 35 mL/min
- Allergy to zoledronic acid
- Hypocalcaemia
- Contraindications for zoledronic acid according to the SPC

Fertility and pregnancy

Pregnancy testing and precautions concerning female fertility will not be relevant since the women participating in the study are postmenopausal. There are no special considerations with respect to the male fertility and treatment with zoledronic acid.

Randomization

The patients will be randomized to infusion of zoledronic acid administered either six (6-month-group, n=20) or nine months (9-month group, n=20) after the last denosumab injection or to observation in the form of monthly monitoring of bone resorption (observation group, n=20). If p-CTX increases above 1.26 ug/l in patients in the observation group or the nine months group, zoledronic acid will be administered. If BMD decreases by more than 5% at any site after three months in the observation group, infusion of zoledronic acid will be administered.

The randomization code will be generated by the hospital pharmacy, Aarhus University Hospital. Participants will be randomized in blocks of 6[4].

[4] In case of dropouts the randomization codes will be reused. The codes will be randomized amongst the new participants.

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

The investigational drug is zoledronic acid 5 mg/100mL - a bisphosphonate for intravenous infusion. Participants will be given a full dose of 5 mg, which is the standard dose for treatment of osteoporosis as an infusion over 30 minutes. The drug will be supplied by the hospital pharmacy and delivered directly to our research facility at Aarhus University Hospital, where we will perform our standard regimen of quality control. The drug will be stored in a locked closet at room temperature. In case of technical problems with the drug it will be replaced, and the drug returned to the pharmacy. Technical problems include discoloration, particles or contamination, leakage, or cracks. The investigator is accountable for the drug. Drugs will be administered according to the randomization. As part of the standard treatment of osteoporosis a daily intake of 1000mg calcium and 38ug vitamin D will be secured by supplementation.

Duration of study

Included patients will be part of the study for up to 30 months. The primary endpoints will be investigated 12 months after infusion of zoledronic acid. The participants will receive a letter from the investigator after the termination of the study with information about the study results.

Study plan

Group 1: 6-month group	Baseline	M1	M3	M6	M12	M16	M20	M24
Informed consent	X							
Medical history	X							
Physical examination	X							
Bone markers	X	X	X	X	X	X	X	X
Biochemistry	X				X			
HR-pQCT	X				X			
DXA	X			X	X			X
Zoledronic acid treatment	X							
Fracture history	X				X			X
Telephone call						X	X	

Group 2: 9-month group	Baseline	M1+2[1]	M3	M4	M6	M9	M15	M19	M23	M27
Informed consent	X									
Medical history	X									
Physical examination	X									
Bone markers	X	X	X	X	X	X	X	X	X	X
Biochemistry	X						X			
HR-pQCT	X						X			
DXA	X		X			X	X			X
Zoledronic acid treatment			X							
Fracture history	X						X			X
Telephone call								X	X	

Group 3: Observation group	Baseline	M1-5[2]	M3	Mx[3]	Mx +1	Mx +2	Mx +6	Mx +12	Mx +16	Mx +20	Mx +24
Informed consent	X										
Medical history	X										
Physical examination	X										
Bone markers	X	X		X	X	X	X	X	X	X	X
Biochemistry	X							X			
HR-pQCT	X							X			
DXA	X		X	X			X	X			X
Zoledronic acid treatment				X							

Fracture history	X							X			X
Telephone call									X	X	

[1] M1 + M2: Month 1 and month 2 after baseline.

[2] M1 - M5: Month 1 to month 5 after baseline.

[3] Mx: months after baseline, depends on when the specified levels of p-CTX or BMD loss are achieved

Investigations

Bone turnover markers: Biochemical markers of bone turnover are s-bone alkaline phosphatase (s-BSAP), p-osteocalcin, p-PINP and p-CTX. The samples will be collected in peripheral blood samples in the morning (7·30–10·45 a.m.) after a minimum of eight hours of fasting, then centrifuged at 400 rpm at five degrees Celsius for ten minutes and stored at -80 degrees Celsius. P-CTX, p-osteocalcin and p-PINP will be analyzed on EDTA plasma using ELISA (Cobas 6000 immunoassay analyser, Roche Diagnostics GmbH) and BASP on serum using immunochemical reaction (ISYS). The samples will be analysed in a batch at the Department of Biochemistry, Aarhus University Hospital to reduce the analytical variation. The precision is ±7·4% at 32 µg/l (95% CI), ±10% at 0·30 µg/l, ±6% at 18 µg/l and ±20% at 44.4 µg/l for p-PINP, p-CTX, p-osteocalcin and s-BSAP, receptively. If the results of any of the blood samples are below or above the detection range, we will use the lowest or highest detectable value, respectively. The BTMs will be measured at every clinical visit. If the specified p-CTX level is reached before month three (nine-months group) or month six (observation group) zoledronic acid will be administered.

Biochemistry: Markers of diseases affecting bone metabolism (calcium, phosphate, magnesium, 25-OH-vitamin D, PTH, creatinine, alkaline phosphatase, TSH). The samples will be analyzed at the Department of Biochemistry, Aarhus University Hospital.

Bone mass: Areal bone mineral density (aBMD) (g/cm^2) of the lumbar spine (L1-L4) and hip (left) will be measured using a Hologic Discovery scanner (Hologic, Inc., Waltham, MA, USA). The right hip was scanned in case of prosthesis at the left hip. All participants were examined on the same DXA scanner throughout the trial. Incident vertebral fractures will be investigated using the vertebral fracture assessment (VFA) tool on the Hologic Discovery scanner. Lumbar spine trabecular bone score (TBS) will be measured using the TBS iNsight software, version 2·1·0·0 (Medimaps, Merignac, France).

Bone quality: Bone microarchitecture and estimated bone strength will be assessed by a high-resolution peripheral quantitative computed tomography (HR-pQCT) scan of the distal radius and tibia.

Treatment: An intravenous infusion of 5 mg zoledronic acid will be administered at study day 0 (6-months group), at month three (9-months group), or depending on increase in p-CTX, decrease in BMD, or the occurrence of an osteoporotic clinical vertebral or hip fracture, but no later than at month 6 (observation group). The patients will be monitored with DXA 6, 12 and 24 months after the infusion of zoledronic acid. Zoledronic acid will be re-administered if BMD has decreased more than 5% at the lumbar spine, total hip or femoral neck. If p-CTX increases above 1.26 ug/l during the 2nd year a second infusion of zoledronic acid will be administered.

Fracture history: Participants will be questioned about incident fractures at months 12, 15, or x+12 and again at months 24, 27, or x+24. Information will be confirmed using discharge notes from hospitals.

Data management

Source data identification and verification

Source data will be entered into the patient file and/or the CRF. Most data will be found both in the patient file and the CRF, but some source data, for example body weight and height will be entered directly into the CRF. This will be specified in the source data file. The investigators, the monitor from the GCP-unit at Aalborg and Aarhus University will perform data verification.

Subject data protection

Access to CRFs will be limited to investigators and other healthcare professionals involved in this study. Data from the patient files 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. The patient files are electronic and kept on the hospital electronic patient file system. Any printouts of the patient files and the CRFs will be kept behind locked doors after working hours.

Data handling

When data analyses is finalized, the data will be converted to an anonymous form using participation numbers only, and names and social security numbers will be removed.

Statistical analysis and power calculation

Baseline characteristics of the three groups will be presented using descriptive analysis and compared using ANOVA and post-hoc unpaired t-tests if ANOVA demonstrates differences between the groups. Changes in bone mineral density one year after the zoledronic acid infusion within groups will be investigated using paired-sample t-tests and compared with the changes reported after stopping denosumab after two years [12] for the three groups combined and individually using one-sample t-test. The proportion of patients who fails to maintain BMD will be compared between groups using chi-sq test. Changes in bone mineral density, HRpQCT measures and markers of bone turnover will be compared between groups using mixed model analysis. Exploratory analyses will include multiple regression analyses aiming at identifying baseline factors or changes occurring at three or six months, which affect the change in BMD one year after the zoledronic acid infusion. Factors included in this analysis will be gender, age, years of treatment with denosumab, baseline BMD, baseline bone turnover markers, change in bone turnover markers three and six months after the zoledronic acid infusion.

Based on a previous study a 5% decrease in lumbar spine BMD can be expected during the first year after discontinuation with a 3% standard deviation [12]. The hypothesis is that treatment with zoledronic acid can decrease this bone loss. Eighteen patients will be needed to demonstrate a bone loss $\geq$ 2.5 % using a paired-sample t-test with a power of 90% and level of significance of 5%. If the decrease is less than that BMD is maintained and the hypothesis can be accepted. To account for dropouts n is increased to 20 in each group. As comparisons between the different treatment regiments suggested in this protocol never have been done before, we cannot estimate differences between groups. However, the least significant change in lumbar spine BMD using DXA is 3%. The SD of lumbar spine BMD in our facility is 3% [18]. To be able to demonstrate a difference in change in lumbar spine BMD between the three groups equal to the least significant change using independent samples t-test we need 16 patients in each group with a standard

deviation of 3%, power of 80% and significance level of 5%. Thus, the already planned 20 participants per group are sufficient to make meaningful exploratory analyses. New participants will be enrolled after four dropouts in total. Per-protocol analysis will be performed.

Recruitment of participants

The patients will be recruited from the outpatient clinics and the DXA units to which patients are referred from their general practitioner at:

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Possible participants will be approached during visits or by letter. Patients with osteoporosis living in the Central Region of Denmark, who have redeemed five or six prescriptions for denosumab in the last three years[5], will be approached by letter. All staff at the outpatient clinics will be informed about the study including inclusion and exclusion criteria. If the patient is interested in receiving further information, he or she will receive written information about the project. Moreover, we will advertise in daily newspapers and on the webpages www.forsøgsperson.dk and www.sundhed.dk. Participants who respond to advertisements will be sent written information. Subsequently, all possible participants will be invited to a meeting to obtain oral information from one of the investigators. Family members or friends are welcome to participate in the meeting as well. Afterwards the possible participant will be given 14 days to consider whether they wish to participate in the study or not, before they sign the consent form. The participants will not take part in the study before the consent form has been signed.

Biobanks

A research biobank will be made during the study. 20 ml of blood (ten glasses of two ml each) will be sampled. The blood samples will be analyzed in batches for changes in bone markers. After the trial has ended, the remaining blood samples will be transferred to another biobank at Aarhus University Hospital and stored for a maximum of ten years before destruction. Participants will be made aware that the biobank is of relation to future research and that blood samples can be destroyed at all times on request of the patient. The participants will be asked to sign a separate consent form before the remaining blood samples are transferred to the research biobanks.

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 unfavorable and unintended sign (including an 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:

[5] Information on redeemed prescriptions for denosumab is obtained though Register of Medicinal Products Statistics.

- 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 though out 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, to be followed up. All queries related to these AEs will be resolved. Cases of chronic conditions, cancer or AEs on-going 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.

Definition of serious adverse events (SAE)

Any untoward medical occurrence that at any dose:

- 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 jeopardise 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 section 4,8 in the public assessment report of zoledronic acid by the Danish National Board of Health (http://www.produktresume.dk/docushare/dsweb/ApplySimpleSearch/Collection-124).

Definition of suspected unexpected serious adverse reactions (SUSAR)

A suspected unexpected serious adverse reaction is an SAE, which is unexpected and regarded as possibly or probably related to the study product by the Investigator.

Reporting of SAEs, SARs, and SUSARs

SAEs and SARs will be reported to the sponsor no later than 24 hours after the investigator has become aware of them. SUSARs that have been deadly or life threatening will be reported to the Danish Health and Medicines Authority no later than seven days after sponsor is notified. No later than eight days after this notification the Danish Health and Medicines Authority 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 Health and Medicines Authority and the Regional Ethics Committee.

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

Reporting to Health Authorities

The investigator is responsible for all required periodic updates to health authorities and expedited reporting of Adverse Events occurring during the performance of the study, in accordance with local regulations and the agreed protocol. The approving Health Authority may have special requests beyond SUSAR reporting. A full report on all events during the study will be made to the National Committee on Health Research Ethics and the Danish Health and Medicines Authority after the study has ended.

Patients are covered by a publicly funded compensation scheme. As usual 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 zoledronic acid comes to the investigator's knowledge. The study will be terminated for single participants if the investigator suspects that the participant will be in risk of serious, life-threatening events if she continues as part of the study.

The patients will be referred to the outpatient clinic at Aarhus University Hospital after termination of the study.

Perspectives

Many patients will reach osteopenic BMD levels on treatment with denosumab, however the treatment effect on bone turnover and BMD has been demonstrated to be reversible and it is therefore important to find out if denosumab treatment can be discontinued and bone mass maintained by other measures. This study will show if the bone mass can be maintained by administrating zoledronic acid and if timing of the first dose of zoledronic acid after last dose of denosumab matters. If bone loss can be prevented by zoledronic acid expenses on otherwise life-long denosumab treatment can be saved and long-term side effects of denosumab (atypical femur fractures and osteonecrosis of the jaw) can be prevented.

Safety and ethical considerations

Puncture of veins for blood sampling can result in a bruise and very rarely in infection. The DXA and HRpQCT examinations result in radiation doses of maximum 120µSv and 24µSv, respectively. This increases the risk of cancer by 0,0007% and the lifetime risk of cancer increases from 25% to 25.0007%. Known side effects to short-term treatment with zoledronic acid include flu-like symptoms that subside within 2-3 days. For a more detailed list of the known side effect see section 4,8 in the public assessment report of zoledronic acid by the Danish National Board of Health (http://www.produktresume.dk/docushare/dsweb/View/Collection-124).

It would have been more scientifically sound to include a placebo group in the study but we believe that it is already proven that patients in this group would lose most or all of the bone gained on denosumab therapy within a year why we believe it is more ethical to do an uncontrolled study.

As mentioned in the background there have been publications on patients who experienced vertebral and multiple vertebral fractures after stopping denosumab. These cases are rare and we aim to reduce this risk further for participants in the present study by monitoring patients bone turnover by monthly measurement of p-CTX, by performing DXA after three months in the observational group and by allowing treatment prior to schedule if bone turnover increases or bone

mass decreases significantly or if a patient suffers an osteoporotic clinical vertebral or hip fracture. We therefore 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 (100.000kr), The P. Carl Petersen's Foundation (533.784kr), The Torkil Steenbeck's Foundation (75.000kr), The Foundation of Vilhelm Pedersen and wife (1.025.000kr), Amgen (2.571.270kr) and Aarhus University (550,000kr) have granted financial support. Additional support will be applied for at other foundations as well. 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 and will be published in the European Clinical Trials Database. 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 studies are conducted according to the final version of the protocol and according to the Helsinki declaration, GCP guidelines, and the Danish Health Law. The Processing of data is carried out in accordance with the Act on Processing of Personal Data and the study will not be initiated until approval has been given from the Danish Data Protection Agency, The Central Denmark Region Committees on Health Research Ethics, and the Danish Health and Medicines Authority. The study will be monitored by the local GCP unit at Aalborg and Aarhus University Hospital (Aarhus University, Olof Palmes Allé 15, 8200 Aarhus N, Denmark) and conducted in compliance with GCP procedures for quality control and quality assurance.

Research plan and facilities

November 2016-October 2017: Recruitment of participants
November 2016-April 2020: Clinical trial on-going
May 2020-October 2020: Analysis and publication

We have all the facilities for the clinical study including DXA- and HRpQCT-scanners. We have experienced research nurses and laboratory technicians and we have access to analyses of biochemical markers at our Department of Clinical Biochemistry.

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