CLINICAL TRIAL PROTOCOL

The Fragility Fracture Trial (FFT): A randomized, double-blind, placebo-controlled trial to investigate whether zoledronic acid prevents new fractures in older adults with a recent non-hip, non-vertebral fragility fracture

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Sponsor/Coordinating Investigator:	Peter Nordström
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This protocol was developed to comply with the *Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT)* guideline (BMJ 2013;346:e7586). The protocol is based on a template of the National QA Network at Clinical Studies Sweden (https://gothiaforum.com/mallar-f%C3%B6r-planering-och-genomf%C3%B6rande-av-kliniska-studier).

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Sponsor/Coordinating Investigator

As sponsor and coordinating investigator, I am aware that I am responsible for ensuring that this protocol includes all essential information for the conduct of the trial. I agree to conduct the trial in compliance with this protocol, the Declaration of Helsinki, ICH GCP (International Council for Harmonization, Good Clinical Practice), and Swedish and European Union regulations.

I will submit this protocol and all other essential study-related documents to the principal investigators and other staff involved in this study, so that they can conduct the study correctly. I am aware that this study will be monitored by an indepdendent monitor and possibly inspected by the Swedish Medical Products Agency.

Sponsor/Coordinating Investigator's signature	Date
Peter Nordström	
Printed name	

Protocol Revision History

Date	Version	Main revisions
2020-04-28	1	
2020-10-04	2	**Sections 7.3 and 9:** Data on physical activity and hand grip strength will be collected at all study centers, not just at those who currently have access to the necessary equipment. **Sections 3.3, 7.3, 9, and 13.6:** Health-related quality of life outcomes have been added. **Section 3.3:** The exploratory objective of comparing the effects of one versus two infusions has removed, as such an analysis may be biased when it is based on a comparison of more and less adherent participants. **Section 3.3:** An exploratory objective has been added to investigate whether there is an interaction effect between zoledronic acid and FRAX score. **Sections 7.1-7.2:** Non-vertebral fracture has been added as a secondary outcome. The outcome of fall without fracture has been redefined to include only falls from standing height or less. International Classification of Diseases codes have been included for all primary and secondary outcomes. **Sections 5.1 and 13.2:** The definition of fall from standing height or less has been specified with ICD-10-SE codes. Falls on stairs or steps have been excluded from the definition. **Section 9:** All baseline testing has been moved to the screening visit so that baseline data will be collected for all patients who provide written informed consent, not only for those who are eligible and randomized. This change also simplifies the randomization visit. Similarly, all testing at Visit 2 (time of second infusion) has been moved to Visit 1 to simplify Visit 2 and to ensure that follow-up data are collected on patients who withdraw from the study because of ineligibility for the second infusion. **Section 9:** Renewal of vitamin D prescriptions may be done at every follow-up contact. Each investigator will decide whether a participant does not need a second loading dose of vitamin D because the participant has taken enough monthly vitamin D. **Section 13.6:** The treatment-by-baseline value interaction terms have been removed from the analysis of covariance models, as their inclusion is not customary. **Section 13.7:** Post-infusion symptoms occurring ≤3 days after each infusion will be presented. **Section 13.1:** The reporting of the recruitment process has been expanded. **Section 6.1:** Premature unblinding will not lead to automatic discontinuation of treatment.

		Sections 10 and 15.9: Participants will be informed of their treatment assignment when they complete follow-up or when they withdraw from the study, instead of at the end of the trial, which may be two years later. **Sections 9 and 15.4:** Participants will have the option of letting a next of kin act as a proxy respondent in follow-up interviews if the participant is unable to respond himself or herself.

Contributions and Contact Information

Name and occupation	Role	Contributions	Contact Information
Peter Nordström, Professor and Chief Physician	Sponsor/coordinating investigator	- Conceived the study - Designed the study - Coauthored this protocol - Applied for funding	- Address: Unit of Geriatric Medicine, Department of Community Medicine and Rehabilitation, Umeå University, 90187 Umeå, Sweden - Phone: +46 70 8996599 - Email: peter.nordstrom@umu.se
Jonathan Bergman, PhD student	Protocol coauthor	- Designed the study - Planned the statistical analysis - Coauthored this protocol	- Address: Unit of Geriatric Medicine, Department of Community Medicine and Rehabilitation, Umeå University, 90187 Umeå, Sweden - Email: jonathan.bergman@umu.se

Roles and Responsibilities

Role	Responsibilities
Sponsor/Coordinating investigator	- Overall responsibility for the trial, including the protocol and monitoring plans - Ensure that the trial follows ICH GCP, the Declaration of Helsinki, and regulations - Ensure that the trial is uniformly conducted across study centers - Guarantee that participants are insured - Obtain funding - Delegate responsibilities - Recruit study centers (principal investigators) - Publish results
Principal investigators (one per study center)	- Ensure that the trial is conducted according to this protocol - Ensure that participants have provided written informed consent - Ensure that eCRFs are complete and accurate - Protect the integrity and safety of participants - Ensure that participants get necessary medical care - Recruit clinical staff - Ensure that staff are adequately trained
Trial statistician	- Write a computer program for generating a randomization list - Develop an electronic case report form (eCRF) - Continuously monitor incoming data for accuracy, completeness, and compliance with the protocol - Conduct a blind review of the trial database - Report to the sponsor when the trial database is accurate and complete - Draft the Clinical Study Report
University Hospital of Umeå Clinical Research Center	- Generate and store a randomization list - Monitor the trial for adherence to GCP, regulations, and ethical guidelines - Assist in reporting SUSARs - Assist in writing DSURs - Assist in developing and maintaining the eCRF - Assist in writing an agreement with a pharmaceutical company - Assist in developing a monitoring plan

Acronyms and Abbreviations

Acronym/Abbreviation	Explanation
AE	Adverse event
DSUR	Data safety update report
eCRF	Electronic case report form
EudraCT	European Union Drug Regulating Authorities Clinical Trials Database
EQ-5D-3L	EuroQol-5 Dimensions-3 Levels
EQ-5D-5L	EuroQol-5 Dimensions-5 Levels
GCP	Good clinical practice
ICD-7-SE	International Classification of Diseases, 7th revision, Swedish Version
ICD-10-SE	International Classification of Diseases, 10th revision, Swedish Version
ICH	International Conference/Council on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
ICMJE	International Council of Medical Journal Editors
ID	Identification
NA	Not applicable
ND	Not done
NK	Not known
SEK	Swedish Krona
SUSAR	Suspected unexpected serious adverse reaction

1. Synopsis

Background: The incidence of fracture is high among older adults, and older adults who sustain one fracture are at high risk of sustaining new fractures. No clinical trial has examined whether bone-protective therapy is effective in preventing new fractures among older adults with a recent non-hip, non-vertebral fragility fracture (i.e., a fracture due to a fall from standing height or less), without prior measurement of bone mineral density.

Primary objective: To investigate whether zoledronic acid (a widely used antiresorptive) reduces the risk of new clinical fractures, as compared with placebo, in older adults with a recent non-hip, non-vertebral fragility fracture.

Study design: 4-year, phase IV, multicenter, parallel-group, randomized, double-blind, placebo-controlled trial.

Study population: Adults aged 65 or older with a non-hip, non-vertebral fragility fracture in the past 2 years. Fragility fracture is defined as a fracture occurring after a fall from standing height or less.

Number of participants: 2900.

Investigational products: Two infusions of zoledronic acid (5 mg) or placebo, one at baseline and one at 24 months. Prior to infusion, participants will receive a loading dose of oral vitamin D (50,000 IU or 2.5 mg). Participants will also be prescribed monthly oral vitamin D (25,000 IU or 1.25 mg/month) for the duration of the trial.

Primary outcome: Time to first new clinical fracture.

Study period: Q1 2021 - Q1 2027.

2. Introduction

About 95,000 individuals suffered a major fracture in Sweden in 2017.[1,2] In comparison, less than half that number, about 40,000, suffered a stroke or myocardial infarction.[1] The most serious type of fracture is the hip fracture, which is regarded as an end stage disease because 25% of hip fracture patients die within a year.[3,4] Of surviving hip fracture patients, only a minority regain their pre-fracture level of physical functioning and quality of life.[5] High mortality rates and reduced quality of life are also seen in patients with vertebral fractures.[6,7] Thus, hip and vertebral fractures are serious threats to the health and independence of older people.

Despite the seriousness of hip and vertebral fractures, these do not constitute the majority of fractures, as they occur in about 28,000 persons per year in Sweden.[1,2] Far more common are fractures of the arm or lower leg, which occurred in about 58,000 people in Sweden in 2017.[1,2] Furthermore, according to government data we have on hand, individuals with a previous fracture of the arm or lower leg have 2.6 times the risk of sustaining a fracture as do individuals without a previous fracture. The data also show that fractures of the arm and lower leg occur at a mean age of 71 years, compared to 77 years for vertebral fractures and 83 years for hip fractures. These facts suggest that health care professionals may be able to prevent hip and vertebral fractures by targeting interventions to older adults with a non-hip, non-vertebral fracture.

Bone-protective agents, such as bisphosphonates, are currently available for reducing fracture risks in older adults.[8] However, the efficacy of these agents after a fracture has not been studied in clinical trials other than after a hip or vertebral fracture.[9] Most trials have recruited participants on the basis of osteoporosis or low bone density (with or without a vertebral fracture),[9] but this approach has the disadvantage that physicians often have limited access to bone densitometry,[10] which complicates treatment decisions in clinical practice. Furthermore, many fracture patients, especially male fracture patients, do not have osteoporosis. The actual percentage of patients who have osteoporosis varies among studies, but hip or spine osteoporosis (T-score $\leq$-2.5) has been reported to be present in 36%,[11] 44%,[12] and 56%[13] of female fracture patients and in 13-15%[11] and 21%[12] of male fracture patients. Another study, which examined appendicular osteoporosis (T-score $\leq$-2.5 in the heel, finger, or forearm), showed that osteoporosis was present in 18% of women with an osteoporotic fracture.[14] Another difficulty in fracture prevention is that health care systems often are not organized to identify patients with osteoporosis. Whereas fractures are initially treated at emergency wards, bone densitometry is usually located in other departments (if available at all) and primary care is often responsible for making treatment decisions.

Given the high incidence of non-hip, non-vertebral fractures, the high risk of recurrent fractures, and the seriousness of hip and vertebral fractures, which occur later in life than other types of fractures, it would be of high interest to study whether bone-protective therapy is effective in older adults who are selected solely for having a history of non-hip, non-

vertebral fracture, without prior assessment of bone mineral density. Increased treatment of this patient group is feasible because only around 10% of Swedish fracture patients aged 50 or older receive treatment.[15,16]

Zoledronic acid is a well-known and well-studied bone-protective agent, which was approved in the European Union in 2005.[17] Zoledronic acid reduces bone resorption and belongs to the bisphosphonate class.[18] In three large clinical trials, zoledronic acid was shown to reduce the risk of clinical fracture in women with osteoporosis, in women with osteopenia, and in men and women with a hip fracture.[19–21] Although a fourth trial conducted in men with osteoporosis did not show a significant effect of zoledronic acid on clinical fractures, this trial was smaller and it did show a significant effect on radiologically detected vertebral fractures.[22]

The most common adverse effects of zoledronic acid are transient post-infusion symptoms (pyrexia, myalgia, headache, arthralgia, and influenza-like symptoms), which occur in about one third of patients in the first 3 days following an initial infusion.[19] These symptoms are less common after subsequent infusions.[19] Zoledronic acid and other bisphosphonates have been associated with two rare but serious adverse effects: atypical femoral fractures and osteonecrosis of the jaw.[23,24] However, osteonecrosis of the jaw does not primarily occur in osteoporosis patients but in cancer patients, who receive much higher doses of zoledronic acid to reduce the adverse skeletal effects of cancer (e.g., bone metastases).[23] In osteoporosis patients, the incidence of osteonecrosis of the jaw is estimated to be 1 in 100,000 to 1 in 10,000.[23] Atypical femoral fractures are also rare, and they are typically reported after long treatment periods of 7 or more years.[25,26] It should also be noted that no increased risk of these adverse events was reported in the four largest trials of zoledronic acid that have been conducted to date.[20–22,26]

3. Objectives

3.1. Primary objective

The primary objective is to investigate whether zoledronic acid reduces the risk of new clinical fractures, as compared with placebo, in older adults with a recent non-hip, non-vertebral fragility fracture.

3.2. Secondary objectives

The secondary objectives are to investigate whether zoledronic acid, as compared with placebo:

1. has a different effect on new clinical fractures in men and women
2. reduces the risk of cancer
3. reduces the risk of cardiovascular disease (stroke or myocardial infarction)

4. reduces the risk of death
5. reduces the risk of falling

Although it is conventional to designate subgroup analyses as exploratory, the subgroup analysis by sex was designated as a secondary objective because no clinical trial has shown that bone-protective therapy significantly reduces clinical fractures in men.[8] This fact may explain part of the low rates of osteoporosis treatment in men.[16,27] Cancer was selected as a secondary outcome to confirm the results of a recent phase IV trial, which showed a significant reduction in cancer (a pre-specified safety outcome) in osteopenic women treated with zoledronic acid.[21] Cardiovascular disease was selected because both clinical trial data and observational data have suggested that bisphosphonates protect against stroke and myocardial infarction.[21,28–30] Death was selected to confirm the results of a phase III trial that demonstrated significantly reduced mortality in hip fracture patients treated with zoledronic acid.[20] Falling was selected as an outcome to confirm the results of two trials, one of denosumab and one of zoledronic acid, which showed significant reductions in falls.[20,31]

3.3. Exploratory objectives

The exploratory objectives are as follows:

1. To investigate whether the effect of zoledronic acid on new clinical fracture decreases with age
2. To investigate the time-to-onset of effect of zoledronic acid on clinical fractures
3. To investigate whether a higher level of physical activity leads to a greater reduction in clinical fractures with zoledronic acid
4. To investigate whether zoledronic increases muscle strength, as compared with placebo
5. To investigate whether the effect of zoledronic acid on new clinical fractures is greater in participants who have a higher 10-year probability of major osteoporotic fracture according to the FRAX fracture risk assessment tool
6. To investigate whether zoledronic acid reduces height loss, as compared with placebo
7. To investigate whether zoledronic acid improves health-related quality of life
8. To investigate whether zoledronic acid reduces the risk of death, cancer, clinical fractures, and cardiovascular disease, as compared with placebo, over 10 years

Efficacy by age was selected as an exploratory objective because some researchers suggest that bone-protective therapy is less effective in the oldest age groups, perhaps because the high incidence of falls offsets beneficial skeletal effects.[32,33] Low treatment rates of osteoporosis have also been observed in the oldest age groups.[34] Efficacy by level of physical activity was selected because it is well known that bone-protective agents have different effects on bone mineral density in different individuals. Given that physical loading decreases the risk of fractures and is necessary for maintaining bone health at all ages,[35] we hypothesize that zoledronic acid will result in a greater increase in bone density, and therefore a greater decrease in fracture risk, in participants who are physically active. Muscle strength is included as an explanatory outcome because it is a possible mechanism for a beneficial effect of zoledronic acid on falls. This mechanism is supported by the known crosstalk between osteocytes and muscle cells, which is mediated by pathways influenced by bone-protective

agents.[36] Height loss was selected because it is related to efficacy concerning vertebral fractures. Height loss was designated as an exploratory outcome because it will only be assessed halfway through the trial and not at the end. A reduction in height loss with zoledronic acid was observed in two previous trials of zoledronic acid.[19,21] Health-related quality of life will be used to assess whether participants perceive any health benefits from zoledronic acid treatment. Health-related quality of life outcomes were specified in the protocol of three previous trials of zoledronic acid.[20–22] The results of one of these trials have been published,[37] and these showed a significant improvement in the EuroQol-5 Dimensions-3 Levels (EQ-5D-3L) visual analogue scale, in which respondents rate their overall health on a scale from 0 to 100 (from worst to best imaginable health). An improvement was not, however, observed in the summary score of the 5 dimensions.[37]

4. Trial Design

The study will be a 4-year, phase IV, multicenter, parallel-group, randomized, double-blind, placebo-controlled trial. A 4-year duration was selected because this is anticipated to capture the greatest anti-fracture efficacy of 2 infusions of zoledronic acid administered at baseline and at 24 months (see Section 6). The trial will be multicenter so that a sufficient number of participants can be recruited. Study centers (one per principal investigator) will be located in major hospitals in Sweden. We anticipate that approximately 10 centers will be needed. A parallel-group, randomized, and double-blind design was selected to enable the study to produce substantial confirmatory evidence of efficacy. The trial will be placebo controlled because there is currently no standard treatment for fracture patients who do not have a hip or vertebral fracture and who have not undergone bone densitometry.

The study is anticipated to take 6 years to complete. Participants will be recruited during the first 2 years, starting in the first quarter of 2021 and ending in the last quarter of 2022. The remaining 4 years will be spent monitoring participants until they have each completed 4 years of follow-up. The last participant's last follow-up contact is planned for the first quarter of 2027. The last participant's last follow-up contact is defined as the End of the Trial.

5. Eligibility Criteria

5.1. Inclusion criteria

To be included in the trial, patients must meet all of the following criteria:

1. Willing and able to provide written informed consent
2. Age ≥65 years
3. Ambulatory (i.e., able to walk without the assistance of another person; canes, walkers, and other assistive devices are permitted)

4. Community dwelling (i.e., living in own home or with friends or relatives)
5. Sustained a non-hip, non-vertebral fragility fracture in the past 2 years

Fragility fractures are defined as fractures occurring after a fall from standing height or less.[10] In particular, these falls include the following International Classification of Diseases, 10th Revision, Swedish Version, (ICD-10-SE) codes:

1) Fall on same level involving ice and snow (W00)
2) Fall on same level from slipping, tripping and stumbling (W01)
3) Other fall on same level due to collision with, or pushing by, another person (W03)
4) Fall while being carried or supported by other persons (W04)
5) Other fall on same level (W18)

If the type of fall is unknown, it will be assumed *not* to have occurred after a fall from standing height or less.

Non-hip, non-vertebral fractures will include fractures of the clavicle, upper arm, forearm, ribs, pelvis, femur (excluding hip), or lower leg. Fractures of the face, skull, hands, and feet will be excluded, because these are not generally considered osteoporotic.[10]

The limit of no more than 2 years since fracture is based on two considerations. The first consideration is that the risk of sustaining a new fracture is highest soon after the initial fracture.[38,39] For this reason, we expect zoledronic acid to have the greatest effect if it is administered as soon as possible. However, setting a short limit would reduce the number of potentially eligible participants, making the trial more difficult to carry out. Therefore, the time limit should not be set too short for pragmatic reasons.

A minimum duration between time of fracture and time of recruitment has not been set, because no delay in fracture healing was observed in a phase III trial of zoledronic acid in hip fracture patients.[20]

5.2. Exclusion criteria

Patients will be excluded from the trial if they meet any one of the following criteria:

1. History of hip fracture or vertebral compression fracture
2. Undergone bone density scanning since the fragility fracture
3. Severe renal impairment (estimated glomerular filtration rate of <35 ml per minute per 1.73 m^2 of body surface area)
4. Remaining life expectancy of <1 year, according the investigator's judgement
5. Hypocalcemia (serum calcium <2.2 mmol/L)
6. Sarcoidosis (contraindication for vitamin D)

7. Previous use of bone-protective drug (e.g., bisphosphonate, teriparatide, denosumab, raloxifene, or strontium ranelate; calcium and vitamin D are acceptable)
8. Use of systemic glucocorticoids at a dose of ≥5 mg (prednisolone or equivalent) for ≥3 months in the past year
9. Other medication or medical condition for which bone-protective therapy is indicated (e.g., bone metastases or use of aromatase inhibitor; osteoporosis is permitted)

Patients with a hip or vertebral fracture will be excluded because these patients should receive bone-protective therapy according to current Swedish national guidelines.[40] Patients who have undergone bone density scanning will be excluded because the inclusion of these patients could skew the study population toward low-risk patients who do not qualify for treatment according to current guidelines, which would reduce the statistical power of the trial.

6. Investigational Products

Zoledronic acid (5 mg) or placebo (normal saline) will be given as a 15-minute intravenous infusion at baseline and at 2 years. The volume of fluid will be 100 ml (5 ml of zoledronic acid or placebo + 95 ml of mannitol, sodium citrate, and water for injections). A flush of 10 ml of normal saline will be given before and after administration, resulting in a total of 120 ml of intravenously infused fluid. All patients will receive advice about nutrition and exercise to prevent new fractures.

Zoledronic acid can cause post-infusion symptoms (pyrexia, myalgia, headache, arthralgia, or influenza-like symptoms) within the first 3 days.[19] Patients will be informed that these symptoms may be uncomfortable but that they are not dangerous and can be eased with paracetamol if needed.

To prevent hypocalcemia, all participants will receive a loading dose of oral vitamin D (50,000 IU or 2.5 mg) 1 week before the first infusion. Participants will also be prescribed monthly oral vitamin D (25,000 IU or 1.25 mg/month), which is to be taken for the duration of the trial. Participants who have not taken their monthly vitamin D will receive a second loading dose 1 week before the second infusion. The sponsor will cover the cost of the loading doses, but participants will be expected to cover the cost of their monthly vitamin D.

The monthly dosage frequency of vitamin D is less frequent than was used in the phase III trials of zoledronic acid.[19,20] A monthly frequency was, however, used successfully in a large phase IV trial.[21] Calcium will not be prescribed because this phase IV trial provided only vitamin D, with successful results.[21] If a participant has not received the loading dose of vitamin D between 1 and 4 weeks before the day of randomization, then both randomization and the first infusion will be delayed until this criterion is met.

The above-mentioned dose and administration route for zoledronic acid were selected based on the design of previous phase III trials and on standard use in clinical practice.[17,19,20] The treatment interval of 2 years is not standard, however, as 1-year intervals were used in the

phase III trials and are commonly used in clinical practice.[17,19,20] Our decision to extend the treatment interval is based on evidence from a phase IV trial that found similar efficacy with 18-month treatment intervals.[21] A smaller trial also demonstrated that the effect of zoledronic acid on bone mineral density peaks at least 24 months after an initial infusion.[41] Furthermore, a post-hoc analysis of two large clinical trials demonstrated similar reductions in clinical fractures in patients who had received only 1 instead of 3 infusions of zoledronic acid.[42] Based on these findings, we expect a 24-month interval to be optimal.

Zoledronic acid and placebo must be stored securely, meaning that it is accessible only to authorized persons and that it is kept in the conditions specified in the Summary of Product Characteristics for Aclasta (the brand name of zoledronic acid).[17] The drugs may only be used for the purposes specified in this protocol. At the end of the study, any remaining products will be handed over to pharmacies for destruction. A drug accountability log will be used to follow the pathway of the study medications throughout the study. At the time of writing, we have not decided on a manufacturer for zoledronic acid and placebo.

6.1. Discontinuation of treatment

The investigators and the sponsor can at any time decide that a participant should not have the second infusion due to, for example, adverse events. A participant will be automatically disqualified from receiving the second infusion if any one of the following criteria is met:

1. Decision of investigator or sponsor
2. Request from participant
3. Withdrawal of the participant from the trial
4. Initiation of bone-protective therapy (other than the assigned investigational product)
5. Severe renal impairment (estimated glomerular filtration rate of <35 ml per minute per 1.73 m^2 of body surface area) at Follow-Up Visit 1
6. Hypocalcemia (serum calcium <2.2 mmol/L) at Follow-Up Visit 1, unless this can be resolved within the time window of the second infusion, i.e., 24 months ± 4 weeks (see Section 9)

A participant's follow-up will continue even if treatment is discontinued, unless the participant wishes to withdraw from the study.

6.2. Concomitant medications

The use of the prescribed vitamin D and of bone-protective medications during follow-up (other than the assigned investigational product) will be reported. The use other concomitant medications during the trial will not be reported, because this is a late-phase trial and no adverse drug interactions are known to exist.[17]

7. Outcomes

7.1. Primary outcome

Due to the high clinical relevance of most fractures, the primary outcome will be time to first new clinical fracture (ICD-10-SE codes: S12-S52, S72, S82, M48.5, M49.5, M80.0A, M80.0J, and M80.0K). Clinical fracture will be defined as any fracture that comes to medical attention, excluding fractures of the facial bones, skull, hands, and feet (ICD-10-SE codes: S02, S62, and S92), which are not generally considered osteoporotic.[10] For the same reason, pathological fractures (e.g., due to cancer or osteomyelitis) will be excluded. High-energy fractures will be included because these are also associated with low bone mineral density.[11,43]

Participants will be asked about fractures at study contacts, which will take place every 6 months of follow-up (see Section 9). Participants will also have the possibility of reporting fractures to their study center between the scheduled contacts. Participants who withdraw will be asked if they wish to answer questions about incident fractures before they formally withdraw. The Swedish Fracture Register will also be used to trace fractures for patients who consent to registry follow-up.

Fractures identified through interview will be verified through review of medical records by the study site investigator, given that the participant consents to it. Due to limited resources, the sponsor/coordinating investigator will not adjudicate fractures or other outcomes. To reduce the amount of missing data in the 10-year post-study analysis, fractures will be traced centrally by the sponsor using the above-mentioned ICD-10-SE codes in the Swedish National Patient Register. This register records all diagnoses made in inpatient care in Sweden since 1987 and all outpatient secondary (i.e., non-primary) care since 2001.[44]

7.2. Secondary outcomes

The secondary outcomes are as follows:

1. Time to first non-vertebral fracture (ICD-10-SE: S22.2, S22.3, S22.4-S22.8, S32.1-S32.5, S42, S52, S72, S82)
2. Time to first new non-hip, non-vertebral fracture (ICD-10-SE: S22.2-S22.8, S32.1-S32.5, S42, S52, S72.3-S72.4, S82)
3. Time to first hip fracture (S72.0-S72.2)
4. Time to first new forearm fracture (S52)
5. Time to first clinical vertebral fracture (S12, S22.0, S22.1, S32.0, M48.5, M49.5, M80.0A, M80.0J, and M80.0K)
6. Time to death

7. Time to first new cardiovascular event (stroke or myocardial infarction) (ICD-10-SE: I21, I60-I64)
8. Time to first new cancer diagnosis (ICD-7-SE: 140-209)
9. Occurrence of fall from standing height or less (ICD-10-SE: W00, W01, W03, W04, W18) not resulting in fracture between baseline and 48 months

Hip fractures are included among non-vertebral fractures and forearm fractures are included among non-hip, non-vertebral fractures. However, hip fractures and forearm fractures will also be assessed separately because these are common and classic types of osteoporotic fractures. Fractures, myocardial infarction, stroke, and cancer events will be identified through self-report and verified by investigators through review of medical records. Participants will also have the possibility of reporting these outcomes to their study center between the scheduled study contacts. Participants who withdraw will be asked if they wish to answer questions about these outcomes before they formally withdraw.

In the 10-year follow-up, myocardial infarction and stroke will be traced using the above-mentioned ICD-10-SE codes in the National Patient Register, SWEDEHEART, and the Swedish Stroke Register. SWEDEHEART is a register that covers most patients in Sweden who are hospitalized for acute coronary syndrome, coronary interventions, or valvular interventions.[45] The Stroke Register is a register of Swedish stroke patients, although it does not have complete coverage of the population.[46] At the 10-year follow-up, cancer events will be identified through the Swedish Cancer Register, which records all new cases of cancer in Sweden since 1958.[47] Deaths will be identified through the Swedish Cause of Death Register and by reports from family members to study centers.[48]

7.3. Exploratory outcomes

Two exploratory outcomes will be assessed:

1. Change in body height (cm) from baseline to 24 months
2. Change in non-dominant hand grip strength (kg) from baseline to 24 months
3. Change in EQ-5D-5L summary score from baseline to 12, 24, 36 and 48 months
4. Change in EQ-5D-5L visual analogue scale from baseline to 12, 24, 36 and 48 months

Body height (without shoes) will be measured in centimeters using stadiometers at baseline and at 24 months. Hand-grip strength will be measured using dynamometers. Values will be rounded to one decimal place. These outcomes will not be assessed at 48 months because the last follow-up visit will be a telephone interview instead of a physical visit to save resources (see Section 9).

The EQ-5D scale will be used to assess health-related quality of life because it is short, generic (rather than disease-specific) and widely used. Two previous trials of zoledronic acid used the 3-level version the EQ-5D (i.e., the EQ-5D-3L),[22,37] but the 5-level version (EQ-5D-

5L) will be used in the current trial so that smaller differences in patient-reported health status can be detected. The summary score will be derived from the Swedish Time Trade-off, experience-based value set.[49] The term "experience-based" refers to the instruction that respondents rate their current health state, rather than a hypothetical health state.[49] The EQ-5D-5L will be administered annually as a compromise between detail in results and time burden for participants. Both the summary score and the visual analogue scale will be rounded to 2 decimal places.

7.4. Safety outcomes

Based on previous trials of zoledronic acid and the Summary of Product Characteristics of Aclasta,[17,19–21] the occurrence or worsening of the following pre-specified safety outcomes will be assessed*:*

1. Post-infusion symptoms
    a. Influenza-like symptoms
    b. Pyrexia
    c. Myalgia
    d. Headache
    e. Arthralgia
2. Osteonecrosis of the jaw
3. Osteonecrosis (avascular necrosis) not of the jaw
4. Atypical femur fracture
5. Any atrial fibrillation
6. Serious atrial fibrillation
7. Re-operation of fracture
8. Delayed fracture healing
9. Renal failure
10. Hypocalcemia
11. Ocular event

In the 10-year follow-up, ICD-10-SE codes will be used to trace occurrences of atrial fibrillation (I48), renal failure (N17-N19), hypocalcemia (E835) femur shaft fractures (S722-S724), ocular events (H10-H22), osteonecrosis not of the jaw (M87), and inflammatory conditions of the jaw (K10.2) in Swedish National Patient Register.

8. Safety

8.1. Adverse events

In addition to the pre-specified safety outcomes, participants will we asked about any adverse events occurring or worsening since the time of infusion. An *adverse event* will be defined as

is done by the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH):[50]

> *Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment.*

The principal investigators or research nurses will interview participants about adverse events at each study contact. The questions will be open-ended, instead of directed at particular types of events. Participants will also have the possibility of reporting adverse events between the scheduled contacts. Participants who withdraw will be asked if they wish to answer questions about adverse events before they formally withdraw.

The following information will be collected about adverse events:

1. Type of event (diagnosis, symptom(s), or abnormal laboratory value)
2. Duration (start date and, if applicable, stop date)
3. Causality (suspected/not suspected to be related to zoledronic acid or placebo)
4. Seriousness (serious/non-serious)
5. Expectedness (expected/unexpected) (applicable only if the event is suspected to be causally related to zoledronic acid or placebo)
6. Actions taken
7. Outcome

The severity of the adverse event (e.g., mild, moderate, or severe) will not be recorded because this information is not legally required and is unlikely to be analyzed.

Participants who have been affected by an AE will be followed-up according to the clinical practice of the study center until the adverse event is resolved or stable. Participants with AEs that are suspected to be related to the investigational product will be followed-up until they have recovered or are well taken care of and on the way to good recovery.

8.2. Serious adverse events

As recommended by the ICH,[50] an adverse event will be classified as a *serious adverse event* if it

- *results in death,*
- *is life-threatening,*
- *requires inpatient hospitalization or prolongation of existing hospitalization, or*
- *results in persistent or significant disability or incapacity.*

As also stated by the ICH,[50]

Medical and scientific judgement should be exercised in deciding whether expedited reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalisation but may jeopardise the patient or may require intervention to prevent one of the other outcomes listed in the definition above. These should also usually be considered serious.

8.3. Adverse drug reactions

An adverse event will be considered an *adverse drug reaction* (i.e., a causal link is suspected) if either the sponsor or the investigator considers there to be a reasonable possibility, based on evidence or arguments, that the event is causally related to an investigational product (zoledronic acid or placebo).[50] This definition of adverse drug reaction excludes adverse reactions to non-investigational products, such as vitamin D or other concomitant medications. If an adverse drug reaction meets the criteria for seriousness, it will be classified as a *serious adverse drug reaction*.[50]

8.4. Unexpected and serious unexpected adverse reactions

An adverse reaction will be classified as an *unexpected adverse reaction* if its nature or severity is inconsistent with the Summary of Product Characteristics of Aclasta.[17,51] If the unexpected adverse reaction is serious, it will be classified as a s*uspected unexpected serious adverse reaction* (SUSAR).[51]

In accordance with EU guidelines (Paragraph 29),[52] investigators must report serious adverse events to the sponsor within 24 hours of becoming aware of them. If the adverse event is a SUSAR, the sponsor will report it to the Swedish Medical Products Agency and to the Swedish Ethical Review Authority.[51] SUSARs that are fatal or life-threatening will be reported within 7 days, and relevant follow-up information will be reported within an additional 8 days. Other SUSARs will be reported within 15 days. The sponsor will inform all principal investigators of SUSARs that occur.

With the help of the University Hospital of Umeå Clinical Research Centre, the sponsor will submit to the Swedish Medical Products Agency an annual Development Safety Update Report (DSUR), listing all serious adverse events and evaluating participant safety, as required by regulations (8 kap. 10 §).[53] The DSURs will comply with the ICH E2F guidelines.[54]

9. Participant Timeline

A participant timeline can be found in Table 1. As shown, potential participants will be invited to a screening visit to provide written informed consent, to be assessed for eligibility, to be assigned a participant identification (ID) code, to undergo baseline testing, and to receive vitamin D. Of these steps, informed consent must come first, followed by assignment of a participant ID code. The baseline tests will include a self-administered health questionnaires (see the variables in Section 13.2) and measurements of body height and body weight (using a stadiometer and a medical scale). In addition, baseline tests of hand-grip strength will be conducted using hand dynamometers. Data on participants' baseline level of physical activity will be collected using hip-worn accelerometers. Participants will be asked to carry such an accelerometer on their non-dominant hip for 7 days. The device should be removed only at night and during showering, bathing, and swimming. The device should be set to record at 30 Hertz with 60 second epoch lengths. At the screening visit, all participants will receive a loading dose of oral vitamin D and a prescription for monthly oral vitamin D (see Section 6).

One week after the screening visit, participants will return for a randomization visit. At this time, participants will also return their accelerometer. The randomization visit may be cancelled by telephone if the results of the blood tests indicate that the participant does not meet the eligibility criteria. In this case, the patient will be informed that his or her participation ends here. If, on the other hand, the participant is still eligible, he or she will be infused with the next available bottle of investigational product. The next available bottle will be determined based on the sequential medication number with which each bottle is labeled. These bottles must be assigned to participants in the order in which they are labeled. The act of selecting a bottle is considered to be the act of randomizing the participant.

Follow-up interviews will be conducted by telephone every six months for 48 months for assessment of outcomes, adverse events, use of the prescribed vitamin D, and use of non-investigational bone-protective therapy. At every second interview, participants will be asked to complete the EQ-5D-5L online. The telephone interviews may be conducted with a next of kin if the participant is unable to respond and if the participant has consented to this. Halfway through the trial, at 24 months, participants will visit their study center for an in-person interview, outcome assessment, and a second infusion of zoledronic acid or placebo. Participants who have not taken their monthly vitamin D, or who have not taken a sufficient amount in the investigator's opinion, will receive a second loading dose of vitamin D one week before the second infusion. The final study contact, at 48 months, will be a telephone interview instead of an in-person visit to reduce the burden on investigators. Participants will be followed through registers for ten years after randomization, so that the long-term effects of zoledronic acid can be evaluated. Participants will be given the choice to opt out of registry follow-up.

Investigators must do their best to ensure that study contacts occur in the designated time windows by scheduling study contacts in good time. To reduce the burden on investigators, telephone interviews will be conducted centrally from the sponsor/coordinating investigator's center. Each visit is anticipated to take 1 hour and each telephone interview 30 minutes.

Table 1. Participant Timeline

	Event										
Timing/procedure	**Scr**	**Rand**	**Tel 1**	**Tel 2**	**Tel 3**	**Vis 1**	**Vis 2**	**Tel 4**	**Tel 5**	**Tel 6**	**Tel 7**
Time point	-7 d	0	6 m	12 m	18 m	23 m + 3 w	24 m	30 m	36 m	42 m	48 m
Time window	-4 to -1 w	0	±4 w	±4 w	±4 w	±4 w	±4 w	±4 w	±4 w	±4 w	±4 w
Informed consent	X										
Eligibility	X	X*				X**	X*				
Participant ID code	X										
Health questionnaire	X										
Body weight	X										
Blood samples	X					X					
Accelerometer	X										
Vitamin D loading dose	X					X†					
Vitamin D prescription	X		X	X	X	X		X	X	X	
Infusion		X					X				
Oral vitamin D use			X	X	X	X		X	X	X	X
Bone-protective drug use			X	X	X	X		X	X	X	X
Adverse event assessment			X	X	X	X		X	X	X	X
Outcome assessment			X	X	X	X		X	X	X	X
Fractures			X	X	X	X		X	X	X	X
Death			X	X	X	X		X	X	X	X
MIMI			X	X	X	X		X	X	X	X
Stroke			X	X	X	X		X	X	X	X
Falls			X	X	X	X		X	X	X	X
Cancer			X	X	X	X		X	X	X	X
Body height	X					X					
Hand-grip strength	X					X					
EQ-5D-5L	X			X		X			X		X

Abbreviations: D, day; EQ-5D-5L, EuroQol-5 Dimensions-5 Levels; M, month; MI, myocardial infarction; Rand, randomization; Scr, Screening; Tel, telephone interview; Vis, visit to study center for follow-up; W, week

*Assessment of laboratory values

** Assessment of qualification for second infusion

† A second loading dose of vitamin D should only be given if the participant has not taken the prescribed monthly vitamin D (or a sufficient amount, in the investigator's opinion)

10. Treatment Allocation and Blinding

Participants will be randomized according to a 1:1 permuted-block design, with randomly varying block sizes. Randomization will not be stratified by study center, so that the investigational products can be distributed from a central location to any study center as needed. To guarantee balance in group sizes within centers, the investigational products will be delivered in boxes containing multiple complete blocks. Centers will obtain investigational products by placing a request to the sponsor, who must authorize delivery from the central location. As zoledronic acid has a limited shelf life, the first and second rounds of treatment will be produced, labeled, and delivered separately.

The trial statistician will use a computerized random number generator to create a randomization list, which will contain a sequential medication number (0001, 0002, etc.) and the corresponding treatment assignment (zoledronic acid or placebo). The randomization list will be sent to the manufacturer of the investigational products, who will label each bottle with a medication number and fill it with the appropriate content. Apart from these numbers, the bottles will be visually identical in terms of content, packaging, labeling, and delivery. If possible, the manufacturer will attach a tear-off label to each bottle, which can be torn off to determine the content of the bottle if emergency unblinding is needed. If this is not possible, each box of investigational products will instead contain sealed envelopes with information about the content of each bottle. These envelopes will only be opened in the case of emergency unblinding, when knowledge of the assigned treatment is necessary to protect participants' health. Investigators will be responsible for registering instances of intentional and unintentional unblinding on electronic case report forms (eCRFs).

As mentioned, the randomization list will be generated using a computer program written by the trial statistician. However, to maintain the trial statistician's blinding, this program will be run by staff at the University Hospital of Umeå Clinical Research Centre. The Research Centre will also be responsible for sending the randomization list to the manufacturer of the investigational products. The randomization list will then be stored by the Research Centre in a locked and safe location. Access to the randomization list will be granted to independent monitors and inspectors upon request, but not to anyone directly involved in the study.

It will not be possible for clinical personnel to predict treatment assignment, because the randomization list will be stored securely and the investigational products will be visually identical apart from the above-mentioned sequential medication numbers. The trial statistician will not reveal the block sizes to anyone else directly involved in the trial (e.g., the sponsor, principal investigators, or investigators' staff).

The study will be double blind. Therefore, the participants, the sponsor/coordinating investigator, the trial statistician, the principal investigators, and the principal investigators' staff will be unaware of the participants' treatment assignment. Participants will be informed of their treatment assignment when they have completed 48 months of follow-up or when

they withdraw from the study. This information will be provided by a research nurse or a member of the administrative staff. The research nurses and administrative staff will obtain information on treatment assignment using the method of emergency unblinding described above (i.e., not by accessing the entire randomization list). They will not spread this information to other staff members, including the principal investigators, the sponsor/coordinating investigator, or the trial statistician. Treatment assignments will be unblinded to other staff at the end of the trial, when the randomization list is unlocked. This list will be unlocked when the sponsor/coordinating investigator and the trial statistician have confirmed that the trial database is accurate and complete and when an analysis dataset has been compiled.

11. Recruitment

Potentially eligible patients will be identified through searching the Swedish Fracture Register for persons who have recently sustained a fracture. The Swedish Fracture Register was established in 2011 to monitor fracture occurrence, fracture care, and health outcomes after a fracture.[55] All patients in this register have agreed to the use of their information in research, although they have not signed consent forms, as this is not required by Swedish law.[55] When potentially eligible patients have been identified through the Fracture Register, they will be contacted through postal mail, followed by a telephone call to ask whether they are interested in participating.

Recruitment through the Swedish Fracture Register has two advantages. First, we consider it to be more respectful than approaching patients in emergency rooms, where they are in pain and in need of medical attention. Second, it will make it easier to recruit the necessary number of participants. If the Swedish Fracture Register has insufficient coverage of fracture patients at a participating hospital, potentially eligible subjects may instead be identified through local patient records (e.g., emergency ward or X-ray records) or fracture liaison services (*Swedish: "frakturkedjor"*).

12. Data Collection

12.1. Participant identification codes

Participants who provide informed consent will be assigned a participant identification (ID) code, indicating the center at which the participant was recruited and a sequential patient number. Once assigned, ID codes will not be reused for new participants. At each study center, participants will also be registered in a participant ID code list, which will link participants' ID codes to their first name, last name, e-mail address, postal address, telephone number, and Swedish Personal Identity Number. Of this information, only the participant ID

codes will be used during data collection and analysis to protect participants' integrity. Participant ID code lists will be sent encrypted to the sponsor to enable telephone interviews every 6 months of follow-up and follow-up through registries.

12.2. Electronic case report forms

The data required to be collected according to this protocol will be entered by investigators onto eCRFs, which will be pseudo-anonymized with participant ID codes. There are two exceptions to this rule, however. First, pseudo-anonymized accelerometer data will be sent to the sponsor for central wear-time validation and physical activity scoring. Second, registry-data will be collected centrally by the sponsor.

All efficacy outcomes and adverse events will be recorded using the ICD-10-SE system. Medications will be recorded using the Anatomical Therapeutic Chemical Classification System. The eCRF has not been created at the time of writing, but once this is done, its location will be specified in subsequent versions of this protocol or in the Clinical Study Report. To ensure that the system is secure, the eCRF system will be set up in collaboration with the University Hospital of Umeå Clinical Research Centre and the Department of ICT Services and System Development at Umeå University.

Investigators must ensure that eCRFs are correct and complete and that reporting takes place within the predefined time windows. An entry on the eCRF should be marked ND (Not done) if the information was not collected, NK (not known) if the information is unknown, and NA (not applicable) if the information does not apply, with appropriate Swedish translations. Any corrections made to an eCRF should be noted, signed, dated, and (if needed) explained.

12.3. Biological specimens

Samples of peripheral venous blood will be collected for analyses of serum calcium and creatinine clearance (i.e., estimated glomerular filtration rate). The total volume of blood taken from each participant will be a maximum of 20 ml (10 ml at the screening visit and 10 ml 1 week before the 24-month follow-up), unless further blood samples are needed to ensure a participant's safety. The samples will be analyzed locally at the accredited department of clinical chemistry at each study center's institution. The samples of venous blood will be destroyed immediately after analysis, but the results will be archived as source documents (see below).

12.4. Documentation

The sponsor will keep a Trial Master File and investigators will keep an Investigator Site File containing the essential documents of the trial, as defined in ICH GCP.[56] These documents will be archived in accordance with each institution's local rules, but for a minimum of 15 years.

As stated in the ICH GCP,[56] principal investigators must keep source documents, which include (but are not limited to) eCRFs, questionnaires, and laboratory reports to enable reconstruction and evaluation of the trial's results. Investigators will also keep a drug accountability log so that investigational products can be tracked and a screening log of the number of persons invited to screening and the number attending screening. The investigator must ensure that all source documents are accessible for monitoring and inspection.

12.5. Data management

The trial statistician will continuously monitor eCRFs for accuracy and completeness (including range and logical checks) and for compliance with this protocol. Any inaccuracies, inconsistencies, or deviations will be reported to the appropriate study center, with a request for a correction or an explanation. The trial database will be backed up regularly. The sponsor/coordinating investigator may also appoint staff to conduct on-site monitoring to verify eCRFs with source documents. A detailed plan for data management has not been developed at the time of writing, but it will be attached to the Clinical Study Report.

13. Statistical Analysis

Statistical analyses will be performed using the latest version of R software. All statistical hypothesis tests that can be two-sided will be two-sided. P-values <0.05 will be considered statistically significant, unless otherwise specified. P-values will be rounded to two decimal places if ≥0.01 and rounded to three decimal places if <0.01 but ≥0.001. P-values <0.001 will be expressed as "<0.001".

The zoledronic acid and placebo groups will be defined according to randomization. Baseline date will be defined as the date of randomization. Follow-up time will be defined as the date of death, withdrawal, loss to follow-up, or last follow-up contact (whichever came first) minus the date of randomization plus 1 day (to account for the possibility of an event later in the day of randomization). Incomplete follow-up will be defined as follow-up time that ends before the last study contact.

13.1. Description of recruitment process

The recruitment process will be described in terms of the number of persons invited to a screening visit, the number who attended a screening visit, the number who provided informed consent, the number who met all eligibility criteria, and the number excluded at screening (in total and by reason for exclusion).

13.2. Baseline characteristics

All randomized participants (i.e., the intention-to-treat population) will be included in an analysis of baseline characteristics, in which the zoledronic acid and placebo groups will be compared. An analysis of baseline characteristics will also be performed for all patients who provide written informed consent but who are not randomized. Baseline values will be defined as the last measurements prior to randomization. The following numeric, binary, and multi-level categorical baseline characteristics will be analyzed:

Numeric:

1. Age, years
2. Body height, cm
3. Body weight, kg
4. Body mass index, kg/m^2
5. Time since quitting smoking, years
6. Time since most recent stroke, years
7. Time since most recent myocardial infarction, years
8. Current dose of oral prednisolone, mg/day
9. Time since most recent cancer diagnosis, years
10. Number of bone fractures in adulthood (age ≥18 years)
11. Time since most recent non-hip, non-vertebral fragility fracture, months
12. Estimated glomerular filtration rate, ml/min/1.73 m^2
13. Serum calcium, mmol/L
14. Hand-grip strength, kg
15. Number of steps/day
16. Time spent sedentary, hours/day
17. Time spent in light physical activity, minutes/day
18. Time spent in moderate-intensity physical activity, minutes/day
19. Time spent in vigorous-intensity physical activity, minutes/day
20. Time spent in very vigorous-intensity physical activity, minutes/day
21. Time spent in moderate- to vigorous-intensity physical activity, minutes/day
22. 10 year probability of major osteoporotic fracture according to the FRAX tool, %
23. 10 year probability of hip fracture according to the FRAX tool, %

Binary:

1. Sex (man, woman)
2. Ever undergone bone density scanning (yes, no)
3. Provided written informed consent (yes, no)
4. Ambulatory (yes, no)
5. Community dwelling (yes, no)
6. History of hip fracture (yes, no)
7. History of vertebral compression fracture (yes, no)
8. Diagnosis of osteoporosis (yes, no)
9. Remaining life expectancy <1 year (yes, no)
10. Ever use of antidepressant (yes, no)
11. Chronic obstructive pulmonary disease (yes, no)
12. History of stroke (yes, no)
13. History of myocardial infarction (yes, no)
14. Rheumatoid arthritis (yes, no)
15. Other disease that is strongly associated with osteoporosis (e.g. gluten intolerance, early menopause (before 45 years of age), chronic liver disease, or chronic gastrointestinal disease) (yes/no)
16. Use of systemic glucocorticoids at a dose of ≥5 mg (prednisolone or equivalent) for ≥3 months in the past year (yes, no)
17. Current use of oral prednisolone (yes, no)
18. Ever use of osteoporosis medication other than calcium or vitamin D (yes, no)
19. Other medication or medical condition for which bone-protective therapy is indicated (yes, no)
20. Parental history of hip fracture (yes, no)
21. Place of the most recent non-hip, non-vertebral fragility fracture (inside, outside)
22. Estimated glomerular filtration rate <35 ml/min/1.73 m^2 (yes, no)
23. Serum calcium <2.2 mmol/l (yes, no)

Multi-level categorical:

1. Type of fall that led to the most recent fragility fracture (ICD-10-SE codes: W00, W01, W03, W04, W18)
2. Regular cigarette smoker (current, former, never)
3. Current number of cigarettes/day (1-5, 6-10, 11-20, ≥21)
4. Frequency of alcohol consumption (never, ≤1 time/month, 1 times/week or every other week, 2-3 times/week, ≥4 times/week)
5. Number of glasses of alcohol on a day of drinking (1-2, 3-4, 5-6, 7-9, ≥10)
6. Diabetes mellitus (yes, type 1; yes, type 2; yes, but do not know type; don’t know; no)
7. Cancer (current, previous, no, don’t know)
8. Skeletal site of the most recent non-hip, non-vertebral fragility fracture (or the site or the most serious fracture, if multiple)
9. Method of recruitment (Swedish Fracture Registry, local hospital registry, other)
10. Study center

The accelerometer data on physical activity will be wear-time validated with activity measured in all three axes and non-wear time defined as proposed by Choi.[57] Data will only be included if the accelerometer has been worn for a least 10 hours a day for at least 4 days. Cut-points for different levels of physical activity will be selected as proposed by Freedson.[58]

Numeric variables will be summarized using means, medians, standard deviations, 25th percentiles, 75th percentiles, minimums, maximums, and number and percent missing. Binary variables will be summarized as number and percent "yes" and number and percent missing. Categorical variables will be summarized as number and percent in each category and number and percent missing. Numeric values and percentages will be rounded to 1 decimal place. All variables will be summarized using number and percent of values out-of-range and, for laboratory values, number and percent outside reference values (see Section 13.7).

13.3. Analysis of investigational products

For each infusion, the following information will be reported by study group for all randomized patients:

1. Receipt of infusion 1, number (%)
2. Receipt of infusion 2, number (%)
3. Receipt of infusion 1 within time window (see Section 9), number (%)
4. Receipt of infusion 2 within time window (see Section 9), number (%)
5. Reason for not receiving infusion 1
6. Reason for not receiving infusion 2
7. Zoledronic acid as infusion 1, number (%)
8. Zoledronic acid as infusion 2, number (%)
9. Placebo as infusion 1, number (%)
10. Placebo as infusion 2, number (%)
11. Receipt of vitamin D loading dose prior to infusion 1, number (%)
12. Receipt of vitamin D loading dose prior to infusion 2, number (%)
13. Time from receipt of vitamin D loading dose 1 to infusion 1, days
14. Time from receipt of vitamin D loading dose 2 to infusion 2, days
15. Time from randomization to infusion 1, days
16. Time from randomization to infusion 2, months
17. Duration of infusion 1, minutes
18. Duration of infusion 2, minutes
19. Interruption of infusion 1, number (%)
20. Interruption of infusion 2, number (%)
21. Reason for interruption of infusion 1
22. Reason for interruption of infusion 2

The numeric variables will be summarized using means, medians, standard deviations, 25th percentiles, 75th percentiles, minimums, and maximums. The categorical variables will be summarized as number and percent in each level. The number and percent with missing values will be calculated for all variables.

13.4. Analysis of follow-up

The number and percent of randomized patients that are contacted at each study contact (visits and telephone interviews) will be reported for the zoledronic acid and placebo groups. The number and percent not completing follow-up will be presented by cause (death, adverse event, loss to follow-up, withdrawal, etc.). Differential follow-up duration between the zoledronic acid and control group will be examined by plotting Kaplan-Meier curves and testing for a difference using the log-rank test. Differences in the number and percent prematurely unblinded will be examined using Fisher's exact test. Number and percent prematurely unblinded by cause (accident, adverse event, or other) will be presented.

13.5. Analysis of concomitant medications

The number and percent of participants receiving an osteoporosis medication (other than the assigned zoledronic acid) during follow-up will be reported. The study groups will be compared using Fisher's exact test. The number and percent reporting use of vitamin D supplements at the required monthly dose will be presented for each study contact. The number and percent reporting complete adherence to vitamin D (i.e. use at every contact) will also be calculated and compared between the groups using Fisher's exact test.

13.6. Efficacy analysis

All randomized patients with non-missing outcome data will be included in an efficacy analysis. For time-to-event outcomes, survival time will be calculated as date of event minus date of randomization plus 1 day (to account for the possibility of an event occurring later in the day of randomization). For participants not experiencing the event, time-to-event will be set as the follow-up time (see definition above). If the date of a participant's time-to-event outcome is incomplete, the date will be imputed as was done in a previous trial.[20] Thus, if the day of the month is missing, it will be imputed as the 15th. If both the day and the month are missing, these will be imputed as July 1. If the entire date is missing, the time-to-event will be set to 1 day. Events that cannot be verified through registries or medical record review will be excluded, but the number and proportion of events not verified will be reported.

For time-to-event outcomes, 4-year cumulative incidence curves will be estimated using the Kaplan-Meier method. Number of persons with an event, numbers of events, and incidence

rates (number of events/total person-years at risk of first event) will also be provided. The efficacy of zoledronic acid will be determined on the basis of the log-rank test. The relative effect of zoledronic acid versus placebo will be represented by hazard ratios (with 95% confidence intervals), estimated using Cox regression. These models will not be adjusted for covariates in the main analysis, so as to be comparable to the log rank test. The proportional-hazards assumption will be assessed using log-minus-log plots and by Wald tests of treatment-by-time product terms. In the case of a clear violation of this assumption, hazard ratios will be computed for time-intervals in which hazard ratios are more stable (e.g. 6-month or 12-month periods). As an additional analysis, the number of participants needed to treat for 4 years to prevent one fracture will be estimated for each fracture outcome using Kaplan-Meier estimated risks. Ninety-five percent confidence intervals will be provided for numbers needed to treat,[59,60] with variance estimates derived using the method proposed by Kalbfleisch and Prentice (p. 18).[61]

The occurrence of falls will be analyzed as the number and percent of participants reporting at least one fall. Falls will not be analyzed as a time-to-event outcome because participants may not remember exactly when they fell. The zoledronic acid and placebo groups will be compared using relative risks, with 95% confidence intervals estimated based on the normal approximation. Participants with incomplete follow-up and who did not report a fall during follow-up will be assumed not to have fallen.

Change-from-baseline outcomes will be analyzed using analysis of covariance. The response variable will be post-intervention value and the explanatory variables will be baseline value and treatment group. For the EQ-5D-5L exploratory outcomes, which will be measured every 12 months of follow-up, an analysis of covariance will be run with each follow-up value as the post-intervention value. To prevent the problem of multiple testing, the stepwise approach to testing described in Section 13.8 will be used. The assumptions of linearity, constant variance, and normality will be checked using residual plots and normal quantile-quantile plots. Clear violations of these assumptions will be dealt with by transformations of the response variable or its baseline value. Clear violations of the assumption of constant variance may instead be dealt with using the method of weighted least squares. Outliers will not be removed. Participants with missing follow-up data on change-from-baseline variables will be excluded.

The hypothesis tests of efficacy will not be adjusted for multiple testing to avoid a large reduction in the power of the trial.

13.7. Safety analysis

All participants who receive at least one infusion will be included in a safety analysis. The occurrence of adverse events by the end of follow-up will be analyzed as the number of events and the number and percent of participants reporting at least one event. These data will

be presented by study group, seriousness, and causality (suspected/not suspected relation to study medication). The study groups will be compared using Fisher's exact test. For post-infusion symptoms occurring ≤3 days after infusion, data will be presented for both infusions in total and for events reported to have occurred ≤3 days after each infusion. In addition to specific adverse events, the composite safety outcomes of any adverse event, any serious adverse event, any serious adverse drug reaction, any unexpected adverse drug reaction, and any suspected unexpected serious adverse reaction will be reported. Laboratory values of serum calcium (low, <2.2 mmol/l; normal, 2.2-2.6; high, >2.6)[62] will be analyzed in a shift table from before the first to before the second infusion. The number and percent with severe renal impairment (estimated glomerular filtration rate <35 ml/min/1.73m^2) at Follow-Up Visit 1 will be presented. The mean and standard deviation change in estimated glomerular filtration rate from before the first to before the second infusion will be presented and compared between the groups using an independent-samples *t* test (Satterthwaite approximation of degrees of freedom).

13.8. Subgroup, sensitivity, and exploratory analyses

Baseline characteristics and efficacy outcomes will be presented in subgroups defined by type of baseline fragility fracture (grouped by the first 3 characters of ICD-10-SE codes), age (65-74, 75-84, or ≥85 year), sex, study center, and FRAX 10-year probability of major osteoporotic fracture. In the efficacy analysis, product terms will be included in regression models to assess interaction of treatment with time since fragility fracture, type of fragility fracture, age, sex, study center, physical activity (mean steps/day), and receipt of one or both infusions. These interaction effects will be tested using Wald tests for numeric and binary variables and likelihood ratio tests for multi-level categorical variables. We do not expect these interaction analyses to show significant differences in effect.

Six sensitivity analyses will be conducted. First, to assess the presence of confounding, regression analyses will be adjusted for the following baseline covariates: age, sex, BMI, study center, time since fragility fracture, and site of fragility fracture (grouped by the first 3 characters of ICD-10-SE code). Second, the efficacy analysis will be rerun in a per-protocol population (i.e., participants who met all eligibility criteria, either died or completed follow-up, and both were qualified to receive and did receive the 2 assigned infusions). Third, efficacy concerning time-to-event outcomes will be analyzed using the Andersen-Gill Cox model for recurrent events.[63] Fourth, in the analysis of the primary outcome, the potential effect of informative censoring (including the competing risk of death) will be assessed by rerunning Cox models under the extreme scenarios that all participants who did not complete follow-up either (1) sustained a fracture at the time of censoring (i.e., were at high risk of fracture) or (2) had complete follow-up with no event (i.e., were at low risk of fracture).[64] Fifth, participants with a history of cancer at baseline will be excluded from the efficacy analysis of new cancers diagnosed during follow-up. Sixth, outcome events not verified by medical records will be included in the efficacy analyses.

To assess the time-to-onset of treatment effect on the primary outcome, Kaplan-Meier curves will be compared using the log-rank test with censoring at months 48, 42, 36, and so on until month 6. To avoid the problem of multiple testing, a fixed-sequence procedure will be used in which the test will first be performed for risk at month 48, then at month 42, and so on until month 6.[65] If a p-value ≥0.05 is obtained, the results of all subsequent tests will also be considered non-significant. Similarly, Cox regression will be used to estimate hazard ratios and 95% confidence intervals, with censoring at month 48, 42, and so on until month 6.

13.9. Interim analysis

No interim analysis will be performed to determine whether the trial should be terminated early. There are four reasons for this design choice. First, the risk of large safety concerns is low due to the fact that the effects of zoledronic acid have already been studied, without major safety concerns, in four large trials.[19–22] In addition, zoledronic acid will be administered only twice, which is less than is commonly done in clinical practice.[17] It should also be noted that zoledronic acid was approved in the European Union back in 2005.[17] Second, the risk of needing to stop due to futility is low, because zoledronic acid has been shown effective in multiple studies.[19–22] Third, early termination for efficacy is unlikely to result in a substantial increase in the number of patients who receive treatment, as treatment rates are currently low[15,16] and treatment decisions are based on local guidelines, which take time to update. Fourth, interim analyses are complicated to carry out, as they require unblinding of the data.[66]

No interim analysis will be performed for the purpose of adjusting the sample size upward, because this would not be feasible due to budget constraints.

13.10. Sample size and power calculations

The trial will enroll 2900 patients, of whom 227 will need to sustain a clinical fracture during follow-up for the study to achieve 90% power to detect a 35% reduction in clinical fractures with the log-rank test (2-sided significance level of 5%). This calculation assumes a 4-year fracture risk of 10% in the placebo group and an overall dropout rate of 5% (due to withdrawal or loss to follow-up, i.e., deaths excluded). The details of the calculation can be found in Appendix 1. Appendix 2 provides a table of required sample sizes under varying assumptions. As shown, the required sample size is sensitive to changes in the assumed hazard ratio and the assumed fracture risk in the placebo group, but it is relatively insensitive to changes in the dropout rate.

To put the assumptions of the sample-size calculation in perspective, we note that 3 of 4 previous large trials of zoledronic acid had 90% power,[19,20,22] whereas the fourth had 80% power.[21] Incomplete follow-up (deaths excluded) was observed in 4% of women with osteopenia (6-year follow-up),[21] 8% of men with osteoporosis (1-year follow-up),[22] 13% of women with osteoporosis (3-year follow-up),[19] and 17% of hip fracture patients (1.9-year

median follow-up).[20] Three of the trials that were powered to demonstrate effects on clinical fractures, and these showed effects of 27%,[21] 33%,[19] and 35%.[20]

The assumed 4-year fracture risk of 10% was derived from data about the Swedish population that we have previously collected from the Swedish National Patient Register. We selected adults in Sweden who were aged 65 to 85 years and who suffered an initial fracture of the arm or lower leg in 2006 (ICD-10-SE codes: S42, S52, or S82). There were 10,361 such individuals who were not prescribed bone-protective treatment over the next 4 years. Their mean age was 74.9 years and 73% were women. Over the 4 years, 10.0% (n=1028) suffered a new fracture at a different skeletal site. We expect the restriction of the analysis to fractures of a different skeletal site to lead to an underestimation of the incidence of new fractures, but the restriction is necessary to avoid counting the same fracture twice. The distribution of fractures by skeletal site was as follows:

1. 457 fractures of the hip
2. 148 fractures of the upper arm
3. 125 fractures of the lower leg and foot joint
4. 117 fractures of the radius or ulna
5. 91 fractures of the lumber spine

The risk of a new fracture was similar in women and men, 10.2% in women and 9.6% in men. Assuming a hip fracture risk of 457/10,361=4.4% in the placebo group and a dropout rate of 5%, recruitment of 2900 participants will give the trial 71% power to detect a 40% reduction[19] in hip fractures and 55% power to detect a 34% reduction[21] in hip fractures (5% level).

14. Monitoring, Inspection, Deviation, and Early Termination

Investigators must allow monitoring and inspection by providing direct access to eCRFs, source data, and other study-specific documentation.

14.1. Monitoring

The trial will be independently monitored by the University Hospital of Umeå Clinical Research Centre before, during, and after the study. The purpose of this monitoring is to ensure that the study is carried out according to the protocol; that the data are collected, documented, and reported in accordance with ICH GCP;[56] and that applicable ethical and regulatory requirements are followed. A Monitoring Plan will be developed jointly by the sponsor/coordinating investigator and the Clinical Research Centre.

The study will not have an independent data and safety monitoring board because no interim analysis is planned (see Section 13.9).

14.2. Inspection

The Swedish Medical Products Agency may inspect the trial. In this case, any study-related data requested by the Agency must be provided according to Swedish regulations (10 Kap. 1§).[53]

14.3. Deviations and serious violations

Deviations from this protocol, ICH GCP, or regulations will be documented by the sponsor and principal investigators and be described in the Clinical Study Report. Deviations will be considered serious violations if they significantly affect, or are likely to affect, participants' safety, participants' integrity, or the scientific quality of the trial. Such violations will be reported by the sponsor/coordinating investigator to the Swedish Medical Products Agency within 7 days (p. 17-18).[67] It is the sponsor's responsibility to judge whether deviations are serious enough to qualify as violations.

14.4. Early termination

The trial may be terminated early if it appears that zoledronic acid is resulting in a large number of SUSARs. In the case of termination, investigators will immediately inform the participants of this and ensure appropriate treatment and follow-up. The Swedish Medical Products Agency will be informed as soon as possible, but no later than 15 days after the decision to terminate (9 kap 2 §).[53] Decisions about early termination are made by the sponsor.

15. Ethics

15.1. Compliance with the protocol, GCP, and regulations

The trial will be performed in accordance with this protocol, ICH GCP,[56] the Declaration of Helsinki,[68] and Swedish and European Union regulations. The purpose of this is to ensure the safety and integrity of the participants and the quality of the data.

The Swedish Medical Products Agency will be informed of the study's completion through the submission of a "Declaration of End of Trial Notification" form no later than 90 days after the end of the trial, i.e., the date of the last participant's last follow-up contact (9 kap, 1 §).[53]

15.2. Research ethics approval

Participant recruitment will not begin before this protocol, an informed consent form, and other information provided to participants have been approved by the Swedish Ethical Review Authority. The protocol will also need to be approved by the Swedish Medical Products Agency (5 kap. 1 §).[53]

15.3. Protocol amendments

Substantial protocol amendments must be approved by the sponsor, the Swedish Ethical Review Authority, and the Swedish Medical Products Agency. The Swedish Medical Products agency defines substantial amendments to the study protocol as those that may affect (1) participants' safety or physical or psychological integrity, (2) the scientific value of the study, or (3) are substantial in any other way.[53] Substantial amendments will not be implemented until they have been approved, unless doing so is necessary to prevent immediate harm to participants, in which case the amendments will be reported as soon as possible (7 kap. 1 §, 8 kap. 2 §).[53] The opinions of all principal investigators will be sought before substantial changes are made. The sponsor will ensure that principal investigators are aware of approved changes and have access to the latest version of the protocol.

Non-substantial changes (i.e., small administrative changes) require only the approval of the sponsor and will be clearly noted in an amended protocol and in the Clinical Study Report. Non-substantial changes will be reported to the Swedish Medical Products Agency upon End of Trial reporting or earlier if substantial amendments are needed.[67]

15.4. Informed consent

The principal investigator at each site must ensure that participants are given adequate oral and written information about the study. Participants should be given time to consider the information provided and an opportunity to ask questions. Participants will be able to opt out of the 10-year registry follow-up. They will also be given the option of providing contact information to a next of kin, who can act as a proxy respondent in follow-up interviews if the participant is unable to respond himself or herself. The written patient information and an informed consent form will be developed and approved by the Swedish Ethical Review Authority. Since the latest version of these documents have not been approved at the time of writing, they will only be appended to the Clinical Study Report.

If a patient chooses to participate, both the patient and the investigator will sign the informed consent form. The patient should receive a copy of the written information and the informed consent form. The informed consent form must be signed before any study-specific activity is performed. According to Swedish regulations,[67] informed consent forms must be collected by

qualified physicians. If new information about participants is to be collected after informed consent has been obtained, participants have the right to reconsider whether to continue their participation.

Participants will have the right to withdraw from the study at any time, without justification, and without any consequence to their future medical care. As recommended by ICH GCP however,[56] participants who withdraw will be asked if they want to provide a reason. Participants who request to withdrawal will be given the options of just stopping treatment or of stopping both treatment and follow-up. If a participant wishes that his or her personal data be deleted, the investigator and the sponsor must delete all records of the participant's name, Swedish Personal Identification Number, and contact information. The remaining data (e.g., the eCRF) will no longer constitute personal data under the European Union General Data Protection Regulation (Article 4 (1)),[69] and these data must be retained. The right to retain research data after participant withdrawal is laid down by Swedish law.[70,71]

15.5. Medical record registration

In accordance with Swedish regulations,[67] investigators must register in participants' medical records that the participants are involved in a clinical trial. These entries must include the following information:

1. The trial is randomized and double-blind.
2. The investigational products are zoledronic acid and placebo (normal saline), given as two intravenous infusions at a dose of 5 mg with two years in between.
3. Monthly oral vitamin D (25,000 IU or 1.25 mg/month) has been prescribed, and a loading dose of vitamin D (50,000 IU or 2.5 mg) has been given.
4. Written informed consent has been obtained.
5. Participant ID code.
6. Medication number of the received investigational product.
7. Instructions for emergency unblinding.
8. Investigational product received (once unblinded).

15.6. Insurance

Participants will be protected by the Swedish Patient Insurance and by the Swedish Pharmaceutical Insurance.

15.7. Confidentiality

Data collected in the trial, whether electronic or in physical form, will be processed so that only authorized persons have access to it. Datasets used for statistical analysis, eCRFs, and questionnaires will be pseudo-anonymized using participant ID codes (see Section 12.1).

15.8. Conflicts of interest

The sponsor/coordinating investigator and authors of this protocol declare that they have no conflicts of interest.

15.9. Post-trial care

Participants will be informed of the treatment they received when they have completed 48 months of follow-up or when they withdraw from the study. Participants in the placebo group will not be offered zoledronic acid because of budget constraints and because treatment decisions should be based on individual assessments made according to local guidelines.

15.10. Data access

Principal investigators will have complete access to the data at their center, but they will not have access to the data of other centers. The sponsor and trial statistician will have access to all participant ID code lists and eCRFs. After the trial, all principal investigators will receive the final, pseudo-anonymized analysis dataset.

16. Dissemination

Within one year after the study's End of Trial date, a summary report of the trial will be completed in accordance with Annex 1 of the ICH E3 guidelines.[72] The summary report will be submitted to the Swedish Medical Products Agency.[67] It will also be posted on the European Union Drug Regulating Authorities Clinical Trials Database (EudraCT). Participants will receive a non-technical summary of the study results. The clinical staff will also receive a summary of the results.

The main results of the trial will be published in a peer-reviewed scientific journal, regardless of whether or not the results show a significant treatment effect. Study centers must not publish their own results, because the results from all centers will be pooled and published jointly. Any exceptions from this rule must be approved by the sponsor. R code for randomization, data management, and analysis will be made publically available at the time of

publication. The clinical study report will also be made publically available at this time, with possible redaction of individual-level data if necessary to ensure the participants' integrity. The pseudo-anonymized final analysis dataset will not be made publically available, because these are still considered personal data under the European Union General Data Protection Regulation (GDPR) and because the risk of identifying an individual, due to the detail of the data, cannot be ruled out.[69]

Co-authorship of the peer-reviewed journal article will be determined based on the recommendations of the International Committee of Medical Journal Editors.[73] After the end of the trial, the principal investigators and the sponsor/coordinating investigator will each make a list of members of their staff who want to be included as authors. These lists must include a statement of which ICMJE criteria for apply to each name on the list, as well as an explanation of how each person meets the criteria. The investigators and the sponsor will jointly assess who on these lists meet the ICMJE criteria. The investigators and the sponsor will also determine the order in which the names will appear in the published article. The final decision of which names will appear and in what order will be the joint decision of all investigators, by consensus if possible, by majority vote if necessary. The sponsor will break a tie should one arise.

17. Risk-benefit evaluation

The main expected benefit of zoledronic acid is a reduced risk of fractures. Based on previous studies, we expect to see a 35% relative risk reduction, corresponding to a 3.5% absolute risk reduction. There are also health economics benefits to consider. Below is an example for hip fractures.

We expect hip fractures to occur in approximately 5% of participants during follow up. With an absolute risk reduction of 1.75% from zoledronic acid (35% relative risk reduction), the numbered need to treat to avoid 1 hip fracture is 57. In clinical practice, the cost of the study drug (two 5 mg infusions of zoledronic acid) is about 300 Swedish Krona (SEK). Additional costs of treatment (e.g., the cost of personnel and blood tests) amount to approximately 500 SEK, meaning that the total cost of treatment is about 800 SEK. Therefore, the estimated cost to avoid one hip fracture is 800*57=45,600 SEK.

This cost of 45,600 SEK can be compared to the estimated hospitalization cost of 100,000 SEK for each hip fracture patient.[74] Furthermore, in the 12 months following the fracture, each hip fracture patient requires subsequent health care and social care for about 400,000 SEK.[74] Thus, there are substantial health economic benefits based only on hip fractures. We expect further cost benefits due to reductions in other types of fractures and increased quality-adjusted life years.

There are also risks involved in participating in this trial. One risk is that of adverse effects. As explained in the Introduction, zoledronic acid causes post-infusion symptoms in about a third of patients, but these symptoms are transient and less common after the second infusion.[19] More serious are the adverse effects of atypical femoral fractures and osteonecrosis of the jaw. These effects are rare, however.[23,24] It should also be noted that increased risks of these events were not reported in four previous large trials of zoledronic acid.[20–22,26] In these trials, zoledronic acid was given at more frequent intervals than is planned in our trial, which reduces the risk of adverse effects in our trial.

Another aspect of ethical concern is that some of the patients in the placebo group likely would have received bone-protective treatment if they had not been included in this trial. However, only about 10% of fracture patients receive treatment,[15,16] and there is currently no standard treatment for fracture patients who (as the patients in the current trial) do not have a hip or vertebral fracture.

There is also a risk of invasion of privacy because we intend to contact potential participants through the registers, primarily the Swedish Fracture Register. However, individuals registered in the Swedish Fracture Register have agreed to the use of their data in research. In summary, we consider the benefits of conducting this study to outweigh the risks, making the trial ethical to perform.

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19. Appendix 1: Sample Size Calculation

The first step in the sample size calculation is to calculate the number of fractures that need to be observed in the trial, because the log-rank test is powered by events rather than participants. According to Schoenfeld,[75] the necessary number of fractures (assuming 90% power, a 2-sided alpha of 5%, and a hazard ratio of 0.65) is

$$\frac{4\left(z_{1-0.05/2}+z_{0.90}\right)^2}{\ln(0.65)^2} = 227.$$

Here, z_p is the p^{th} quantile of the standard normal distribution and $\ln(\cdot)$ is the natural logarithm.

The second step is to estimate the required number of participants, ignoring any early dropouts due to withdrawal. According to Schoenfeld,[75] a 10% fracture risk in the placebo group and a hazard ratio of 0.65 corresponds to an estimated risk of

$$1-(1-0.10)^{0.65} = 0.06619$$

in the zoledronic acid group. With 227 fractures, the required number of participants becomes

$$\frac{227}{(0.10+0.06619)/2} = 2732.$$

The third step is to adjust the sample size of 2732 for dropouts. As suggested by Freedman,[76] this can be done simply by dividing the sample size by the proportion of non-dropouts:

$$\frac{2732}{1-0.05} = 2876.$$

For simplicity, we round this number up to 2900.

20. Appendix 2: Sample Sizes Under Varying Assumptions

Required sample size under varying assumptions (5% significance level)				
Power (%)	**HR**	**Risk placebo (%)**	**Dropout (%)**	**Required Sample size**
80	0.65	15	5	1432
			10	1512
			15	1600
		10	5	2154
			10	2274
			15	2408
	0.70	15	5	2022
			10	2134
			15	2260
		10	5	3040
			10	3210
			15	3398
90	0.65	15	5	1912
			10	2018
			15	2138
		10	5	2876
			10	3036
			15	3216
	0.70	15	5	2708
			10	2858
			15	3026
		10	5	4074
			10	4300
			15	4554

Abbreviation: HR, hazard ratio