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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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's/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 that 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 a possible 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 (ICD) 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 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, instead of 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 for 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 has taken enough monthly vitamin D not to require a second loading dose of 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 reported. **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 Main Phase 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.
2021-01-15	3	**Section 4 and 17:** The start of the trial has been delayed. **Sections 4 and 9:** The End of Trial has been redefined as the 10-year registry follow-up. **Section 5.1:** An inclusion criterion has been added to ensure that principle investigators are authorized to verify self-reported outcomes through medical records.
2022-05-06	4	**Sections 6 and 9:** Monthly vitamin D will not be prescribed. Instead, all participants will receive a loading dose of vitamin D before each infusion. Participants will also be recommended to have a sufficient intake of calcium and vitamin D. Participants will not receive advice about nutrition and exercise for preventing fractures, due to limited evidence of effectiveness. **Section 6.1:** Participants with hypocalcemia or hypercalcemia will be disqualified from receiving the second infusion. **Section 6:** The ingredient list for zoledronic acid is redundant and has been deleted. **Sections 7.1 and 7.2:** ICD-10 code T08 has been added for vertebral fractures. **Sections** 7, **9, 13.6, and 15.4:** To increase the efficiency of the study, all outcome events will be collected through registries and medical records, instead of through participant interview. Participants will not be able to opt out of the 10-year registry follow-up, unless they withdraw from the trial entirely. Data will not be collected from SWEDEHEART, the Swedish Stroke Register, or the Swedish Cancer register, as data on myocardial infarction, stroke, and cancer are all available from the National Patient Register. **Section 7.2 and 13.6:** Falls will be analyzed as a time-to-event outcome, since registry-data provide exact dates of falls. **Sections 9 and 15.4:** Participants who develop cognitive or physical disabilities that prevent continued in-person follow-up or telephone interview will be followed-up through registries and medical records only. Next of kin will not be interviewed. **Section 11:** The routines for excluding participants during the trial have been clarified.

		Section 7.4: Possible cases of atypical femoral fracture or osteonecrosis of the jaw will be verified by medical record review. ICD-10-SE codes have been included for pre-specified safety outcomes. Serious atrial fibrillation has been removed as a safety outcome, as data on adverse event severity will not be collected. The five different post-infusion symptoms have been collapsed to one safety outcome. **Section 8.1:** It has been clarified that actions taken in response to adverse events are actions that concern the investigational products, not other actions. **Sections 3.3, 9, 12.2, 13.2, 13.8:** For simplicity, baseline data on physical activity will not be collected. **Sections 3.3, 13.2, 13.8:** For simplicity, the exploratory objective to investigate a possible interaction effect between zoledronic acid and the FRAX score has been removed. The FRAX score is less useful when, as in the current study, bone mineral density is not assessed. **Section 13.2:** The baseline variables have been updated. **Section 13.3:** The analysis of investigational products has been simplified. **Section 5.1:** The inclusion criterion requiring that participants consent to medical-record review of their self-reported outcomes has been removed, as this requirement is covered by the criterion on informed consent. It has been clarified that "age ≥65" refers to age at the time of fracture. **Section 11:** During recruitment, it will be optional for investigators to follow up postal invitations with telephone calls. **Section 7.2:** Non-melanoma skin cancer will be excluded from the cancer outcome, so that this outcome is consistent with the outcome in a previous trial (also see Section 3.2). **Section 12.1:** It has been clarified that registry data will be pseudo-anonymized using participant ID codes. **Section 16:** A Clinical Trial Report will be compiled at both the end of the Main Phase and the end of the Secondary Phase (the End of Trial). The main results will be disseminated at the end of the Main Phase. **Section 4:** The sponsor/coordinating investigator will set up a Coordinating Center. **Sections 9 and 11:** Central follow-up will not be conducted due to the risk of logistical problems. **Section 5.1:** ICD-10-SE codes have been added for fractures.

		Section 5.2: Hypercalcemia and malabsorption of calcium and/or vitamin D have been added as exclusion criteria. **Sections 10 and 13:** The randomization and analysis will be stratified by study center. **Section 9:** The number of follow-up contacts has been reduced to simplify the trial. We do not believe this poses a safety risk, as zoledronic acid is widely used and participants will be able to report adverse events by telephone throughout the Main Phase. **Sections 7.3, 9, 13.6:** Due to the reduction in the number of follow-up contacts, the EQ-5D-5L will be administered less frequently. **Section 9:** Participants will be given a card with study information to carry in their wallet. **Section 3.2:** The possibility of a greater effect on new clinical fractures in women than in men, rather than just a difference in effect, will be investigated.
2021-06-24	5	**Section 6.1:** Adverse events should only lead to discontinuation of treatment if the sponsor/principal investigator so decides. It has been clarified that premature unblinding is not a criterion for discontinuing treatment. **Section 10:** The procedure for emergency unblinding has been described in greater detail.

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 - Set up a Coordinating Center - 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
COVID-19	Coronavirus disease 2019
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-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
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, 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: 10-year, phase IV, multicenter, parallel-group, randomized, double-blind, placebo-controlled trial. The 10 years will be divided into a double-blind Main Phase of 4 years and an open-label Secondary Phase of 6 years.

Study population: Persons with a non-hip, non-vertebral fragility fracture in the past 2 years and who were aged 65 years or older at the time of fracture. 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 each first infusion, participants will receive a loading dose of oral vitamin D (100,000 IU or 2.5 mg).

Primary outcome: Time to first new clinical fracture.

Study period: 2021 – 2033.

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 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; while fractures are initially treated in emergency rooms and orthopedic 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 (that is, 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 greater effect in reducing the risk of new clinical fractures in women than in men
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, we designated the subgroup analysis by sex 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 phase IV trial, which showed a significant reduction in cancer (a pre-specified safety outcome, excluding non-melanoma skin cancer) 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 zoledronic increases muscle strength, as compared with placebo
4. To investigate whether zoledronic acid reduces height loss, as compared with placebo
5. To investigate whether zoledronic acid improves health-related quality of life, as compared with placebo
6. To investigate whether zoledronic acid reduces the risk of death, cancer, clinical fractures, falls, 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 in these groups offsets beneficial skeletal effects.[32,33] Low treatment rates of osteoporosis have also been observed in the oldest age groups.[34] Muscle strength is included as an explanatory outcome because this is a possible mechanism for a beneficial effect of zoledronic acid on falls. Such a mechanism is supported by the known crosstalk between osteocytes and muscle cells, which is mediated by pathways influenced by bone-protective agents.[35] Height loss was selected because it reflects efficacy in reducing vertebral fractures. Height loss was designated as an exploratory outcome because it will only be assessed halfway through the Main Phase but 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,[36] 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 EQ-5D-3L summary score of the 5 dimensions.[36]

4. Trial Design

The study will be a 10-year, phase IV, multicenter, parallel-group, randomized, double-blind, placebo-controlled trial. The 10-year follow-up period will be divided into a double-blind Main Phase of 4 years, followed by an open-label Secondary Phase of 6 years. During the Main Phase, participants will actively participate in the study by receiving investigational products and by being followed-up through study contacts (telephone interview and in-person visits). 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 Secondary Phase will be a 10-year follow-up through registries and medical records, without study contacts.

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. The sponsor/coordinating investigator will also set up a Coordinating Center. 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 12 years to complete (2021 – 2033). Participants will be recruited during the first 2 years. The following 4 years will be spent completing the Main Phase for each participant. The final 6 years will be spent completing the Secondary Phase for each participant. The End of Trial is defined as the date when registry data are obtained for the 10-year follow-up (that is, 10 years after the last participant has been recruited).

The initial plan was to start enrolling participants in the first quarter of 2021. This start has been delayed until the second half of 2021. The start may be delayed further if the sponsor considers participant enrollment to be unsafe due to the coronavirus disease 2019 (COVID-19) pandemic, which broke out in 2020 (see Section 17).

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. Ambulatory (i.e., able to walk without the assistance of another person; canes, walkers, and other assistive devices are permitted)
3. Community dwelling (i.e., living in own home or with friends or relatives)
4. Sustained a non-hip, non-vertebral fragility fracture in the past 2 years
5. Age ≥65 years at the time of fracture

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 all fractures other than of the face, skull, hands, and feet, as these are not generally considered osteoporotic.[10] In particular, the following fractures will be included (ICD-10-SE):

1. Ribs/sternum/bony thorax (S22.2-S22.8)
2. Pelvis (S32.1-S32.5)
3. Shoulder/upper arm (S42)
4. Forearm (S52)
5. Femur, excluding hip (S72.3-S72.4)
6. Lower leg (S82)

The limit of no more than 2 years since the fracture is based on two considerations. First, the risk of sustaining a new fracture is highest soon after the initial fracture.[37,38] Therefore, we expect zoledronic acid to have the greatest effect if it is administered as soon as possible. However, setting a short time limit would reduce the number of potentially eligible participants, making the trial more difficult to carry out. Therefore, the second consideration is that 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/hypercalcemia (serum calcium <2.2 or >2.6 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. Malabsorption of calcium and/or vitamin D (e.g., due to gastric bypass)
10. 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.[39] Patients who have undergone bone density scanning will be excluded because the inclusion of these patients might 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. At each infusion, the volume of fluid will be 100 ml. 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.

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

To prevent hypocalcemia, all participants will receive a loading dose of oral vitamin D (100,000 IU or 2.5 mg) before each infusion. The first loading dose will be taken 1 to 4 weeks before the first infusion, but the second loading dose will be taken on the same day as the second infusion, as the risk of hypocalcemia will be lower if the first infusion was administered without causing hypocalcemia. Participants will be recommended to have a sufficient daily intake of calcium (≥1 g/d) and vitamin D (≥20 µg or 800 IU/d) throughout the Main Phase, and they will be reminded of this before the second infusion.

In two previous trials, a loading dose of vitamin D was given only before the first infusion of zoledronic acid or placebo.[20,21] In the first trial, the loading dose of 50,000-125,000 IU was followed by daily vitamin D and calcium supplements.[20] In the second trial, a loading dose of 100,000 IU was followed by monthly vitamin D supplements (with a recommendation for a calcium intake of ≥1 g/d).[21] A third trial used no loading dose but provided daily calcium and vitamin D.[19] We believe that a loading dose of 100,000 IU before each infusion will be sufficient to prevent hypocalcemia, with little or no additional benefit of continued vitamin D supplementation. There is also evidence that high doses of vitamin D increase the risk of falls and fractures.[40]

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 an 18-month treatment interval.[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. 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.

6.1. Discontinuation of treatment

The investigators and the sponsor can at any time decide that a participant should not receive 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. Wish of participant
2. Decision of sponsor/principal investigator due to adverse event
3. Initiation of bone-protective therapy (other than the assigned investigational product)
4. Severe renal impairment (estimated glomerular filtration rate of <35 ml per minute per 1.73 m^2 of body surface area)
5. Hypocalcemia/hypercalcemia (serum calcium <2.2 or >2.6 mmol/L)
6. Decision of sponsor/principal investigator for other reason

It should be noted that premature unblinding is *not* a criterion for discontinuing treatment. 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 non-investigational bone-protective medications during follow-up will be assessed. The use other medications will not be assessed, because this is a post-marketing 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. Clinical fracture will be defined as any fracture that comes to medical attention, excluding fractures of the facial bones, skull, hands, and feet, 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]

Fractures will be traced centrally by the sponsor through the National Patient Register using ICD-10-SE codes S12-S52, S72, S82, M48.5, M49.5, M80.0A, M80.0J, M80.0K, and T08. The National Patient Register records all diagnoses made in inpatient care in Sweden since 1987 and all outpatient secondary (i.e., non-primary) care since 2001.[44] Data on fractures will also be collected locally at each study center using medical records and the Swedish Fracture Register (same ICD-10-SE codes as above). Fractures identified through registers will be verified through medical records.

7.2. Secondary outcomes

The secondary outcomes are as follows (ICD-10-SE):

1. Time to first non-vertebral fracture (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 (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, M80.0K, T08)
6. Time to death
7. Time to first new cardiovascular event (stroke or myocardial infarction) (I21, I60-I64)
8. Time to first new cancer diagnosis, excluding non-melanoma skin cancer (C00-C43, C45-C97)
9. Time to first fall from standing height or less (W00, W01, W03, W04, W18) not resulting in fracture

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 osteoporotic fractures.

Fractures, myocardial infarction, stroke, cancer, and falls will be traced through the National Patient Register using the above-mentioned ICD-10-SE codes. Fractures will also be traced through medical records and the Swedish Fracture Register (same ICD-10-SE codes). Deaths will be identified centrally by the sponsor through the Swedish Cause of Death Register[45] and locally at study centers through medical records and reports from family members. Apart from fractures, the secondary outcomes will not be verified through medical records, so that the burden on investigators is reduced.

7.3. Exploratory outcomes

Four 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 24 and 48 months
4. Change in EQ-5D-5L visual analogue scale from baseline to 24 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 in kilograms using dynamometers. Each participant will make two attempts, and the maximum value will be analyzed. 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 due to budget constrains (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).[22,36] We will use the 5-level version (EQ-5D-5L) 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.[46] The term “experience-based” refers to the instruction that respondents rate their current

health state, rather than a hypothetical health state.[46] 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, the brand name of zoledronic acid,[17,19–21] the occurrence or worsening of the following pre-specified safety outcomes will be assessed:

1. Post-infusion symptoms (T88.7)
2. Osteonecrosis of the jaw (K10.2)
3. Osteonecrosis (avascular necrosis) not of the jaw (M87)
4. Atypical femur fracture (S722-S724)
5. Atrial fibrillation (I48)
6. Re-operation of fracture
7. Delayed fracture healing (M84.2)
8. Renal failure (N17-N19)
9. Hypocalcemia (E835)
10. Ocular event (H10-H22)

During the Main Phase of the trial, data on safety outcomes will be self-reported, and investigators will ask only open-ended questions about adverse events (see Section 8). The above-mentioned ICD-10-SE codes will be used to trace adverse events in the Swedish National Patient Register at the 10-year follow-up. Medical records will be examined to assess whether femur shaft fractures have atypical features and whether an inflammatory conditions of the jaw are cases of osteonecrosis of the jaw. These assessments will be made by physicians who are blind to treatment assignment.

8. Safety

8.1. Adverse events

An *adverse event* will be defined as is done by the International Council/Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH):[47]

> *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.*

Participants will also be inquired about adverse events at study contacts. The questions will be open-ended, instead of directed at particular events. Participants will also have the possibility

of reporting adverse events by telephone between the scheduled contacts. Participants who withdraw will be asked if they wish to report adverse events before they formally withdraw.

The following information will be collected about adverse events:

1. Description (free text or pre-specified text [see Section 7.4])
2. ICD-10 code (if available)
3. Duration (start date and, if applicable, stop date)
4. Causality (suspected/not suspected to be related to zoledronic acid or placebo)
5. Seriousness (serious/non-serious)
6. Expectedness (expected/unexpected) (applicable only if the event is suspected to be causally related to zoledronic acid or placebo)
7. Actions taken with respect to investigational products (zoledronic acid or placebo)
8. Outcome
9. Comments/other actions

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. Causality will be assessed as a binary variable (suspected/not suspected), because more detailed assessments are not needed to flag potential adverse drug reactions.[48]

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 an 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,[47] 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,*
- *results in persistent or significant disability or incapacity,*
- *or is a congenital anomaly or birth defect.*

As stated by the ICH, adverse events may also be serious for other reasons:[47]

> *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).[47] This definition of adverse drug reaction excludes adverse reactions to non-investigational products, such as concomitant medications. If an adverse drug reaction meets the criteria for seriousness, it will be classified as a *serious adverse drug reaction*.[47]

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.[49] If the unexpected adverse reaction is serious, it will be classified as a s*uspected unexpected serious adverse reaction* (SUSAR).[49]

In accordance with EU guidelines (Paragraph 29),[50] 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.[49] 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 §).[51] The DSURs will comply with the ICH E2F guidelines.[52]

9. Participant Timeline

A participant timeline for the 4-year Main Phase 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 a loading dose of vitamin D. Of these steps, informed consent must come first, followed by the assignment of a participant ID code. The baseline tests will include the EQ-5D-5L, a self-administered health/lifestyle questionnaire (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. Participants will receive a card with study information (e.g., contact information to the center, the participant's participant ID) to carry in their wallet. All participants will also take home a loading dose of oral vitamin D (see Section 6). They will be instructed *not* to take the vitamin D until study staff have notified them that this is safe to do based on the results of their blood tests. Participants must take the loading dose 1 to 4 weeks prior to the randomization visit (see below).

Approximately 10 days after the screening visit, participants will return for a randomization visit. 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 (without follow-up of any kind). If, on the other hand, the participant is still eligible, he or she will be randomized and be infused with zoledronic acid or placebo.

Participants will be encouraged to report adverse events by telephone throughout the Main Phase (48 months). At 24 months, participants will visit their study center to receive a second loading dose of vitamin D and a second infusion of zoledronic acid or placebo. They will also take the EQ-5D-5L, undergo measurements of body height, body weight, and hand-grip strength, and be interviewed about adverse events and non-investigational bone-protective therapy. One week before the second infusion, participants will undergo new blood tests of serum calcium and creatinine clearance. Investigators may choose to refer participants to primary care for blood tests.

The final study contact, at 48 months, will be a telephone interview about adverse events and use of non-investigational bone-protective therapy. The participant will also be asked to complete the EQ-5D-5L through an e-mail link. This link will save the participant's responses directly to the eCRF, so that sensitive information is not transferred via e-mail. Participants who are unable to complete the EQ-5D-5L online will receive a paper version by postal mail.

Investigators must do their best to ensure that study contacts occur in the designated time windows by scheduling the study contacts in good time. Each visit is anticipated to take 1 hour and each telephone interview 30 minutes.

Table 1. Participant Timeline for the 4-Year Main Phase

Timing/procedure	**Scr.**	**Rand.**	**Vis. 1***	**Vis. 2**	**Tel.**
Time point	-10 d	0	23 m + 3 w	24 m	48 m
Time window	-4 to -1 w	0	±4 w	±4 w	±4 w
Informed consent	X				
Participant ID	X				
Inclusion/exclusion criteria	X				
Health/lifestyle questionnaire	X			X	
Body height	X			X	
Body weight	X			X	
Blood samples	X		X		
Vitamin D loading dose	X			X	
Infusion		X		X	
Use of other bone-protective therapy				X	X
Adverse events				X	X
Hand-grip strength	X				
EQ-5D-5L	X			X	X

Abbreviations: D, day; EQ-5D-5L, EuroQol-5 Dimensions-5 Levels; M, month; Rand., randomization; Scr., screening; tel., telephone follow-up; Vis., follow-up visit: W, week
*This visit may be replaced with a referral to primary care for blood tests

10. Treatment Allocation and Blinding

Participants will be randomized according to a 1:1 permuted-block design, with randomly varying block sizes and stratification by center. 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 trial statistician will use a computerized random number generator to create a randomization list. To maintain the trial statistician's blinding, the randomization program

will be run by staff at the University Hospital of Umeå Clinical Research Centre, who will also select a random seed for the program. The Clinical Research Centre will be responsible for uploading the randomization list to the electronic case report form (eCRF), which will have a randomization feature. The randomization list will be stored by the Clinical 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. The Clinical Research Centre will also restrict access to the randomization feature of the eCRF to designated staff members.

The study medications will be purchased as marketed (i.e., in the original packaging). Therefore, principal investigators are responsible for enforcing strict routines to ensure that the trial is double blind. This will be done by designating particular staff members (randomization staff) to be responsible for randomizing participants and preparing infusions. Zoledronic acid will be prepared by replacing part of the content of a 100 ml bottle of normal saline with 5 mg of zoledronic acid concentrate, which is colorless. For the placebo group, infusions will be prepared by breaking the seal of a 100 ml bottle of normal saline, making it visually identical to a bottle of diluted zoledronic acid.

The randomization staff will be responsible for concealing the content of the infusion bottles from all other staff members and from participants. Furthermore, they will not enroll participants or collect follow-up data. All other study staff will be blind to treatment assignments, which includes the sponsor/coordinating investigator, the principal investigators, the trial statistician, research nurses, and administrative staff.

It will not be possible for randomization staff to predict future treatment assignments, because the randomization list will not be accessible to them. In addition, the randomization feature on the eCRF will not include information about future treatment assignments.

Emergency unblinding can be performed if knowledge of a participant’s treatment is essential for ensuring his or her safety. Decisions to emergency unblind a participant are made by the principal investigator or the sponsor/coordinating investigator. In such cases, the principal investigator or sponsor/coordinating investigator will contact the randomization staff at the participant’s study center or designated staff at the Clinical Research Centre (the latter will have access to the treatment assignment of all participants). These staff members will have around-the-clock, online access to participants’ treatment assignment through the eCRF. Investigators will be responsible for registering instances of intentional and unintentional unblinding on the eCRF.

Participants will be informed of their treatment assignment when they have completed 48 months of follow-up (the Main Phase) or when they withdraw from the study. This information will be provided by the randomization staff. The randomization staff will not spread this information to other staff members, who will be blinded until the end of the trial, when the randomization list is unlocked by the Clinical Research Centre. This will be done

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 and Exclusion

Potentially eligible patients will be identified through the Swedish Fracture Register. This register was established in 2011 to monitor fracture occurrence, fracture care, and health outcomes after fracture.[53] All patients in this register have agreed to the use of their information in research, although they have provided written consent, as this is not required by Swedish law.[53] When potentially eligible patients have been identified through the Fracture Register, they will be contacted through postal mail. The invitation will include information about the study, a link to an online informational video, and contact information for reporting interest in participating. To increase participation rates, investigators may follow-up postal invitations with a telephone calls.

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

The principle investigator or the sponsor/coordinating investigator can at any time exclude a participant from the entire trial. A participant may also be excluded from specific parts of the trial (infusions, in-person visits, telephone interview, or follow-up through registries or medical records). Reasons for exclusion may be adverse events (e.g., cognitive disability), death, loss to follow-up, termination of the study center, or participant withdrawal. Discontinuation of infusions is not a sufficient reason for excluding a participant from continued follow-up (see Section 6.1).

12. Data Collection

12.1. Participant identification codes

Participants who provide informed consent will be assigned a sequential participant identification (ID) code, indicating the participant number. Once assigned, ID codes will not be reused for new participants. At each study center, participants will also be registered in a

participant log, 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, in order to protect participants' integrity. Participant lists will be sent encrypted to the sponsor to enable registry follow-up. The registry data will be pseudo-anonymized using the participant ID codes.

12.2. Electronic case report forms

The data that are required to be collected according to this protocol will be entered by investigators onto eCRFs, which will be pseudo-anonymized with participant ID codes. The exception to this rule is registry data on secondary outcomes, which will be collected centrally by the sponsor. However, fractures outcomes will be recorded on an eCRF, as these data will be verified through medical records.

All efficacy outcomes and adverse events will be recorded using the ICD-10-SE system. The eCRF will be appended to 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. Any corrections made to an eCRF should be 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). Further blood samples may be taken 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.[54] 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,[54] investigators must keep source documents, which include (but are not limited to) eCRFs, questionnaires, laboratory reports, and registry data 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 persons screened, invited to a screening visit and the number attending a screening visit. 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 correction or 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. In the Main Phase, follow-up time will be defined as 48 months or the date of death or withdrawal (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 at 48 months. In the Secondary Phase, follow-up will be extended to 10 years.

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, the number excluded at screening (in total and by reason for exclusion), and the number randomized.

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 participants who provide written informed consent but are not randomized. Baseline values will be defined as the last measurement made 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. Age at quitting smoking, years (if former smoker)
6. Number of cigarettes smoked on an average day (if current smoker)
7. Age at time of most recent stroke, years
8. Age at time of most recent myocardial infarction, years
9. Age at most recent cancer diagnosis, years
10. Number of bone fractures in adulthood (age ≥18 years)
11. Date of baseline fracture
12. Creatinine clearance (estimated glomerular filtration rate), ml/min/1.73 m^2
13. Serum calcium, mmol/L
14. Hand-grip strength, attempt 1, kg
15. Hand-grip strength, attempt 2, kg
16. Hand-grip strength, maximum of attempts 1 and 2, kg

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. Sustained a non-hip, non-vertebral fragility fracture in the past 2 years (yes, no)
7. Age ≥65 years at the time of fracture (yes, no)

8. Undergone bone density scanning since the baseline fracture (yes, no)
9. History of hip fracture (yes, no)
10. History of vertebral compression fracture (yes, no)
11. Ever diagnosis of osteoporosis (yes, no)
12. Remaining life expectancy <1 year (yes, no)
13. Ever use of antidepressant (yes, no)
14. History of stroke (yes, no)
15. History of myocardial infarction (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. Previous use of bone protective drug (yes, no)
18. Malabsorption of calcium and/or vitamin D (yes, no)
19. Other medication or medical condition for which bone-protective therapy is indicated (yes, no)
20. Place of the most recent non-hip, non-vertebral fragility fracture (indoors, outdoors)
21. Severe renal impairment (yes, no)
22. Hypocalcemia/hypercalcemia (yes, no)
23. Ever smoker, i.e. smoked ≥100 cigarettes in lifetime (yes, no)
24. Current smoker (yes, no)
25. Non-dominant hand (left, right)

Multi-level categorical:

1. Type of fall that led to the baseline fracture (fall on same level involving ice and snow; fall on same level from slipping, tripping and stumbling; other fall on same level due to collision with, or pushing by, another person; fall while being carried or supported by other persons; other fall on same level)
2. Frequency of alcohol consumption (never, ≤1 time/month, 2-4 times/month, 2-3 times/week, ≥4 times/week)
3. Number of glasses of alcohol on a typical day of drinking (1-2, 3-4, 5-6, 7-9, ≥10)
4. Diabetes mellitus (type 1, type 2, no)
5. Cancer (current, previous, no)
6. Skeletal site(s) of baseline fracture (femur excluding hip, shoulder/upper arm, pelvis, ribs/sternum/bony thorax, lower leg, forearm)
7. Method of recruitment (Swedish Fracture Registry, local hospital registry, participant initiative, other)
8. Study center

The variables on alcohol consumption are derived from the Alcohol Use Disorders Identification Test. A glass of alcohol corresponds to approximately 12 grams of pure alcohol.[55] The variables on cigarette smoking are based on definitions used in previous studies.[56,57]

Numeric variables will be summarized using means, medians, standard deviations, 25th percentiles, 75th percentiles, minimums, maximums, and number missing. Binary variables will be summarized as number and percent "yes" and number missing. Categorical variables will be summarized as number and percent in each category and number 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, number (%)
2. Date of infusion
3. Time from randomization to infusion, days/months
4. Receipt of infusion within time window (see Section 9), number (%)
5. Main reason for not receiving infusion (wish of participant, participant discontinuation, death, exclusion due to adverse event, severe renal impairment [<35 ml/min/1.73m^2], hypocalcemia/hypercalcemia [serum calcium <2.2 or >2.6 mmol/L], use of other bone-protective therapy, decision of sponsor/principal investigator for none of the above reasons)
6. Receipt of vitamin D loading dose prior to infusion, number (%)
7. Reason for not receiving vitamin D loading dose, free text

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 with missing values will be calculated for all variables.

13.4. Analysis of follow-up

The number and percent of randomized patients participating in study contacts will be reported for the zoledronic acid and placebo groups at each study contact. The number and percent not completing study contacts will be presented by cause (death, adverse event, loss to follow-up, termination of study center, withdrawal, other). The number and percent not completing registry and medical-record follow-up will also be presented by cause (death or withdrawal). Differential follow-up duration between the zoledronic acid and control groups 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 (mistake, adverse event, or other) will be presented.

13.5. Analysis of concomitant medications

The number and percent of participants receiving bone-protective therapy (other than the investigational zoledronic acid) during follow-up will be reported. The study groups will be compared 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.

For time-to-event outcomes, 4-year cumulative incidence curves will be estimated using the Kaplan-Meier method. The number of participants with an event, the number of events, and the incidence rates (number of events/total person-years at risk) will also be provided. The efficacy of zoledronic acid will be determined based on the log-rank test, which will be stratified by center. The relative effect of zoledronic acid versus placebo will be estimated by hazard ratios (with 95% confidence intervals) calculated using Cox regression, with stratification by center. 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). The assumption of no interaction between treatment effect and center effect will be tested using treatment-by-center product terms with a likelihood ratio test.[58]

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]

Change-from-baseline outcomes will be analyzed using analysis of covariance. The response variable will be the post-intervention value and the explanatory variables will be baseline value, treatment group, and center. For the EQ-5D-5L exploratory outcomes, which will be measured twice during 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 (i.e., the safety population) 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 2 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 (if a participant has multiple baseline fractures, then the most serious type of fracture in the following descending order of severity will be used: femur

excluding hip, shoulder/upper arm, pelvis, ribs/sternum/bony thorax, lower leg, forearm), age group (65-74, 75-84, or ≥85 year), sex, and study center. 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, and study center. 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, time since fragility fracture, and site of fragility fracture (femur excluding hip, shoulder/upper arm, pelvis, ribs/sternum/bony thorax, lower leg, or forearm). 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 were both 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] with stratification by study center. 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).[58] Fifth, participants with a history of cancer at baseline will be excluded from the efficacy analysis of new cancers diagnosed during follow-up. The same will be done for cardiovascular disease. Sixth, fractures 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 center-stratified 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.[64] If a p-value ≥0.05 is obtained, the results of all subsequent tests will be considered non-significant. Similarly, center-stratified Cox models will be used to estimate hazard ratios and 95% confidence intervals, with administrative 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 choice in design. 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 the trial 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. Furthermore, this would reduce the power of the trial to detect effects on secondary outcomes. Fourth, interim analyses are complicated to carry out, as they require unblinding of the data.[65]

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 participants, 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 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 on the Swedish population that we have previously collected from the Swedish National Patient Register. From this 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 next 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 this 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% significance 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 Main Phase of the study (see Section 4). 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;[54] 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§).[51]

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).[66] It is the sponsor's responsibility to determine 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 §).[51] 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,[54] the Declaration of Helsinki,[67] 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 Trial (9 kap., 1 §).[51] The Swedish Ethical Review Authority will also be notified.

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 §).[51]

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.[51] 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 §).[51] 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 changes are needed.[66]

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. The written patient information, the online informational video, and the informed consent form will be approved by the Swedish Ethical Review Authority. These documents will 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,[66] informed consent must be obtained by a qualified physician. 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,[54] participants who withdraw will be asked if they want to provide a reason. Participants who request 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 be personal data under the European Union General Data Protection Regulation (Article 4 (1)),[68] and these data must be retained. The right to retain research data after participant withdrawal is laid down by Swedish law.[69,70]

15.5. Medical record registration

In accordance with Swedish regulations,[66] 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. A loading dose of vitamin D (100,000 IU or 2.5 mg) has been given.
4. Written informed consent has been obtained.
5. Participant ID.
6. Instructions for emergency unblinding.
7. 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 in electronic or 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

There will be no post-trial care at the end of the Main phase or Secondary Phase. Instead, participants will be informed of the treatment they received when they have completed the 4-year Main Phase 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 at other centers. The sponsor and trial statistician will have access to all participant lists and eCRFs. All principal investigators will receive the final, pseudo-anonymized, analysis datasets.

16. Dissemination

A Clinical Study Report of the trial's results will be completed twice in accordance with Annex 1 of the ICH E3 guidelines.[71] The first time will be within a year after the end of the Main Phase. The second time will be at the end of the Secondary Phase (i.e., the End of Trial). The second report will be submitted to the Swedish Medical Products Agency.[66] 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 when the last participant after the Main Phase of the trial. Clinical staff will also receive a summary of the results.

The results of the Main Phase will be published in a peer-reviewed scientific journal after the completion of the Main Phase, regardless of whether or not the results show a significant treatment effect. The results of the Secondary Phase will be published similarly. 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 Reports will also be made publically available, with possible redaction of individual-level data if this is necessary to ensure the participants' integrity. The pseudo-anonymized analysis datasets will not be made publically available, because these are still considered personal data under the European Union General Data Protection Regulation (GDPR), as the risk of identifying an individual, due to the detail of the data, cannot be ruled out.[68]

Co-authorship of the peer-reviewed journal articles will be determined based on the recommendations of the International Committee of Medical Journal Editors.[72] In good time before publication, the principal investigators and the sponsor/coordinating investigator will each make a list of the members of their staff that 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 principal 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 on the published article. The final decision of which names will appear and in what order will be the joint decision of all principal 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.[73] Furthermore, in the 12 months following the fracture, each hip fracture patient requires subsequent health care and social care for about 400,000 SEK.[73] Thus, there are substantial health economic benefits based on prevented hip fractures alone. 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 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 had they not been included in the trial. However, only about 10% of fracture patients currently 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 addition, we consider it to be more respectful than approaching patients in clinics, such as emergency rooms, where they are in pain and in need of medical attention.

A final risk is the COVID-19 pandemic, which started in 2020 and is ongoing at the time of writing. Due to the participants' age, they are at increased risk of developing severe COVID-19. We believe this risk outweighs any potential benefit of the trial, so participant enrollment will not begin until the pandemic is under control. The sponsor will determine when it is safe to start enrollment. In summary, we consider the benefits of conducting this study to outweigh the risks when the COVID-19 pandemic is under control, 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,[74] 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,[74] 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,[75] 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